

Transcript: SickKids VS Brain Injury

Introduction

Hannah For centuries, it was thought that the brain could not be fixed. Once damaged, brain cells were considered as good as lost and with them, the movements, thinking, and memories they make possible. Brain injury at any age was a tragedy but particularly so for children. Slowly, science has chipped away at this idea through relentless questioning and testing. Maybe injured brain cells would never regrow, but could we convince the remaining brain cells to pick up the slack? Or maybe we could find a way to restart and harness the process that grew the brain in the first place?

Don Every question you answer in science leads to like 10 more new questions.

Freda I always say to people in my lab, it's just as much work to ask a small question as a big question. So given that that's the case, why don't you ask that big blue sky question?

Hannah This is a story about a group of scientists who are asking one of the biggest questions out there: can we heal the brain? And about one family working with them who has a big stake in the answer. You're listening to SickKids VS where we take you to the frontlines in the fight for child health. I'm Hannah Bank, and this is SickKids VS Brain Injury.

Act One: Survival

Hannah Can you tell me a little bit about Tobin? Just his personality and you know what it's been like to be, to be his mom?

Karen It's hard to think of Tobin, remember prior to his first cancer diagnosis, but Tobin inspires me. I know I'm mom, but he inspires me just with his determination, his perseverance, his drive.

Hannah Karen Haas marvels at her 22-year-old son Tobin's perseverance. In 2002 at age two, he was diagnosed with a rare brain tumour that required emergency surgery to save his life.

Karen So you imagine your child really, really sick and really fragile, and you just want to scoop them up and hold them. We couldn't do that. We could hold him, but it had to be at a certain elevation and we had to have a nurse coming in to help every time. He wasn't very verbal then, but he just said home. He just wanted to go home, so we finally got home. And then when we had to go back for chemo, we he handled it as well as a two and a half year old toddler could handle such a vile concoction of chemicals. And then we were able to do a lot of the chemo on an outpatient basis. It meant a lot of driving, but still was home in bed every night. Tobin did have complications from the chemo, which just because of infection, but he handled all that well, and as far as the radiation, radiation wasn't easy but Tobin's attitude was OK. This is part of the day. We just we drive in. He goes to sleep for the radiation. He wakes up in his own room at SickKids. And he had his breakfast and then we marched out of there and we scared the pigeons on the way. There's actually a lot of pleasant memories because well our approach was OK, but this is life, so we're going to make the most of it. And that was that was treatment. It was it was like a job to get through.

Hannah Unfortunately, Tobin's cancer returned when he was five and again when he was nine. By the time he was 10, he had endured three major brain surgeries, 20 months of chemotherapy and 63 radiation treatments. His thyroid is permanently damaged, and he has lost the ability to hear out of his right ear but his grit remains. Karen credits the team at SickKids for helping Tobin and her family make it through those incredibly difficult years.

Karen We called them Tobin's tumour team. They became closer than family. We saw them almost every single day, and they were responsible for keeping Tobin alive and giving him, giving us hope.

Hannah The team also helped the family with what came next. Tobin had survived cancer, but he still had a long road ahead.

Karen At some point, neuropsychology became part of his care and that's actually when we met Dr. Don Mabbott.

Act Two: The Cost of the Cure

Hannah Don Mabbott wears a few different hats at SickKids. He's a senior scientist and head of the Neurosciences and Mental Health Program at the SickKids Research Institute, but he's also a clinical psychologist, which is how he got his start.

Don The bulk of my work has been in children with brain tumours who have been cured of their primary disease, the brain tumour, but have been left with long-term health effects. As a psychologist, a neuropsychologist, I'm particularly interested in understanding the impact of brain tumours and their treatment on kids' thinking and learning.

Hannah Forty years ago, this kind of clinical practice didn't exist. Most kids didn't survive cancer. Thanks to treatment advances in recent decades, today, most children do, but it comes at a cost.

Don The treatment itself does have an impact on the brain, and it causes things like difficulties remembering information, challenges in how kids can solve problems. And these all add up so that kids often have problems at school. You know, completing high school can be a challenge. I can probably count on one hand the number of kids that I've seen who went on to university and completed university.

Hannah These days, any comprehensive cancer program like the one at SickKids has what's called an aftercare clinic. It's where kids who have survived cancer, meet with a team who monitors them for late effects of their cancer treatment. These effects might include stunted growth, organ damage, problems with hearing and vision, risk of secondary cancers and one that's particularly devastating and common among brain tumour survivors, challenges with learning and memory. These latter challenges stem from diffuse injury to the brain caused by chemotherapy and radiation.

Don There are really no primary therapies for dealing with these late effects. The work that I would do helping families is really about helping to cope with these late effects. So if a kid has thinking problems often, it's about helping identify a diagnosis for them of a learning disability and then working with the school to help set up accommodations and find different strategies to help accommodate their learning needs, as opposed to some direct therapy.

Hannah In short, psychologists like Don can offer ways to cope with the side effects of radiation, but they can't actually fix the side effects. I asked Karen what it was like to learn that the life-saving treatment her son needed might also dramatically alter his future.

Karen We knew that surgery was critical to Tobin's survival. Really, it was when we were presented with the this might happen, this might happen, this might happen. It's OK. Yeah, yeah, yeah. Where do I sign? But certainly when it came to radiation, we were super alarmed. It was, is this really necessary? And yet it was required to give Tobin the best hope for a long life.

Hannah I asked Don what it's like to be on the other side of the conversation, explaining to families what lies ahead?

Don It's a challenging conversation, absolutely. It depends on the family. Some families are actually thankful because at least they have a plan. Other families, it is very hard for them to hear because all that they expected of their child and all that they'd hope for their child and their potential growth has been called into question.

Hannah Don vividly recalls one such conversation that would change the course of his career.

Don There was one father in particular, who after we'd had this conversation about the impact of treatment for his daughter, he approached me later.

Hannah Don was doing what he usually did at the time, meet with the family, assess their daughter, identify her strengths, but also her challenges resulting from treatment. Explain that while it is good news that your child has been cured of her brain tumour, unfortunately, she's going to have learning challenges and there's not much we can do to help her recover, but we can help you cope.

Don I remember getting an email from him after we'd had this meeting with the family, he said, you know that, I'm sorry, Dr. Mabbott, but that's just not good enough. There has to be some way that we can actually make a significant difference for my daughter and ultimately all the kids that we're seeing. And he started sending me articles about...these are all things in pre-clinical stages and early basic research about drugs or activities that might help the brain grow again. And it was really that interaction that really prompted me to start saying, well, hey, wait a minute, this isn't good enough. I think we have to start thinking about the late effects in the same way we think about the primary disease. How do we treat the late effects so that ultimately I'm put out of a job so that we don't need me to do these assessments because we can treat the actual late effects and help kids overcome the cost of the cure that we talked about.

Hannah Spurred by his patient's father, Don started exploring ways to repair the brain and latched onto some studies from the 1960s.

Don There was a lot of literature in pre-clinical work, so in animal models, that showed that actually if you had animals and you had a mouse, for example, and put a running wheel in their cage, if they use that wheel compared to say a mouse who didn't have a running wheel, you start to see changes in the brain and the growth of new cells. And I started reading that work and started looking at some work in adults who are aging and the use of exercise to help delay the effects of Alzheimer's. And I realized there might be a way in which exercise can be used to harness the innate ability of the brain to regrow and recover

itself. Being a psychologist, having a behavioral intervention made a lot of sense. So I started looking at exercise as a means for brain repair, exercise as a means to help children recover from these cognitive late effects.

Hannah Don set up a clinical trial looking at the impact of 12 weeks of physical exercise on children treated for brain tumours. And lo and behold.

Don We saw improved ability to think quickly. We saw brain growth. And so that was quite exciting to me.

Hannah Don is being humble. It wasn't just exciting for him. It was exciting for a lot of people. Don was invited to speak about his findings at conferences. One such invitation turned out to be fortuitous.

Act Three: When Don Met Freda

Hannah Don wasn't the only researcher at SickKids trying to heal the brain. While Don was running his exercise clinical trial, a scientist named Freda Miller was discovering something equally earth-shattering.

Freda I'm a neuroscientist who studies the brain, and in particular I study how the brain develops, and then we ask whether we can use lessons that we learn from studying the developing brain to actually repair the injured or degenerating brain.

Hannah Freda originally trained in what she describes as hard core molecular biology biochemistry, but then.

Freda I realized I wanted to do something a little bit more meaningful to me as a person. And I think the biggest mystery and something all of us think about, not just scientists, is how our brain functions to make us what we are. So what does consciousness mean? Why do we sleep? Why do we feel emotions? And it was those kinds of giant questions about, in essence, what it means to be human that made me think, wouldn't it be fascinating to study the brain?

Hannah So that's what she did. She became a stem cell biologist. I could try to explain what that means but Freda does it better.

Freda So if you think about development, we all start out basically as a small mass of cells, quite remarkably, and those cells somehow build our entire bodies, including our brains. Now, the cells that are responsible for building those tissues are what we call stem cells. And I view stem cells as being kind of like the parent cells, you know, the parent cells, you make children. And in this case, the children would be the cells that build the circuitry in your brain. And those children go off and do their jobs. Stem cells are incredibly important because they're the foundational building block during development.

Hannah For a long time, the scientific consensus was that stem cells built the brain during development and then disappeared around age 20, the time when our brain reaches its prime. But then a scientist discovered that stem cells continue to live in the brain throughout our lives in a region important for learning and memory. For Freda, this finding opened the door for her own landmark discovery. She was trying to figure out how the brain is built during development. It was 2010 and Jing Wang, a fellow in her lab, had just made an important discovery about the mechanism that convinces stem cells to make

different types of daughter cells. That might have been the end of the story. But at the same time, a colleague of theirs published a paper saying that the same mechanism that they had just identified could be turned on by a surprising agent, a drug called metformin that is used to treat type 2 diabetes.

Freda So it was at that point that we were actually brainstorming in a group meeting and the idea came up that, wow, do you think that metformin could actually turn on this pathway in the brain and convince new cells to be made and in so doing make us smarter? And we all kind of laughed a little bit at the idea because it seems so out there. But then when we thought about it, it came to us that, well, you know, maybe it's a little out there, but it's certainly worth at least asking if that could be a reality. And that's the work that Jing did next. She basically asked if metformin could cross through into the brain and if it could, whether it would turn on these brain stem cells I've been telling you about. And remarkably, it did exactly that. At that point, we really almost couldn't believe it, but we said, well, I wonder if that has any functional consequences.

Hannah The team was skeptical, but decided to give it a shot. So they joined forces with another SickKids scientist to see if giving metformin to a mouse would make it, well, smarter.

Freda In fact, it did improve a certain kind of learning and memory. And it was at that point that we published a paper on this. And as I said, it was almost too good to be true but we did it a million times. And that started to set the stage for asking about whether that would have any clinical relevance whatsoever.

Hannah So let's get back to Don at the aftercare clinic, where Freda's discovery had the potential to be highly clinically relevant. Don didn't know Freda at the time, but her work had attracted his attention. Her stem cell discoveries had huge implications. And Don was keen to meet her. That's why when he spotted Freda in the SickKids atrium one morning, he introduced himself.

Don She's a famous scientist. This was when I started the exercise stuff. I was quite interested in the stem cell biology stuff. She and her husband, David, were getting coffee and I was like, hey, excuse me. I know you're a famous neurobiologist. Can you sign my lab book? That kind of was what set things up for the conference, I think.

Hannah Both Don and Freda had been invited by a SickKids colleague to present their work at the same conference.

Don She was invited to give a talk on her work in helping the brain repair itself. And she's an excellent speaker. And then I get up and give my talk. And Freda's sitting in the front row. And she's just like, dialed in to the talk. I just I remember that. And then I talk about our promising findings about how exercise can help the brain grow. You know, we think it's because of its impact on the stem cells, but we don't know have any way of measuring that in the human brain. We're seeing these improvements in cognition. And then after the end of the talk, we just kind of both got up and we're like, you know, we need to talk.

Freda He said to me, Freda, this is a safe drug. Do you think we could try to use metformin to treat the kids I see every day, who are these survivors of brain tumours who do have some deficits in some of their cognitive functions?

Hannah SickKids breakthroughs are only possible with the incredible support of our donors. That's why we're proud to recognize CIBC as the premier partner of the SickKids VS podcast. The bank and its team members care about making a difference. CIBC has championed SickKids for over 30 years and is the largest corporate supporter of the SickKids cancer sequencing program. CIBC also generously supports SickKids through CIBC Miracle Day and an active employee giving and volunteer program.

Act Four: It Takes a Team

Hannah Freda and Don had the seeds of a major breakthrough but they knew they needed to prove they could regrow the injured brain. A team coalesced around advancing metformin as a brain repair agent because it was already approved for use in children and they could start a clinical trial right away.

Freda My lab actually is not an expert in asking about repairing the injured brain, but I have a really wonderful close friend and colleague, Cindi Morshead, who is an expert in that. And she works on mice, but she works on fixing the brains of injured mice. And so I was able to turn to Cindi and say, Cindi, do you think you would be interested in working with us to ask if metformin can actually, at least in mice, promote brain repair?

Hannah Cindi said yes.

Freda We put together a team to move from the very basic science that my lab does all the way up to a pilot clinical trial in this special population of children.

Don And so we would get together as a team and write a proposal to do this work. It's a lot of brainstorming, a lot of saying, OK, what does this look like? And you slowly build the shell of a research idea that asks fundamental questions and parallel clinical questions. And there's these parallels across the board. So one of the outcomes of that is Cindi Morshead studied metformin in a mouse model of radiation, which was a clear parallel to the population of kids that I work with. And then we said, OK, we need to look at mouse memory and human memory and there were clear parallels so that we could make translations. And if you saw something in the mouse well that would, what would that look like in the human? And that just gives much more power to any of the findings that you have. So that part didn't happen by accident. That part was very a lot of planning, a lot of meetings, a lot of conversation, ultimately writing a research grant and then getting that research grant funded through various sources.

Hannah Don, Freda, Cindi and their teams were approved for a three-year Brain Canada grant in 2012, but it came with a catch. They needed to find additional funding to match it. Luckily, the Garron Family Cancer Centre at SickKids had a matching fund program and was able to fill the gap. They cleared all the ethical approvals and then they were on their way.

Don It was a small trial. And the thing people need to know about clinical trials is they're very incremental. You start off in small steps and slowly build up the evidence. Before you do the big multimillion dollar trial. You want some evidence that there's promise here. Our goal wasn't to actually answer the big question of does metformin work? It was a may it work? Is it safe in this population? Is it feasible to do this trial? And then is there a signal there that will help us design a future large trial? But we looked at metformin and compared it to a placebo. And we looked at changes in the brain using MRI, a brain imaging technique, and we looked at areas of thinking that we, one, knew were areas that

were compromised in kids treated for brain tumours like memory and like a speed of thinking, but also areas that we had a good sense that might be related to the mechanism of action of metformin. If metformin worked on the hippocampus and made new neurons there, and the hippocampus is important for memory, then we'd expect to see improved memory.

Hannah One of the participants in the feasibility trial was Tobin, who you heard about earlier. He was 12 years old at the time, and though his cancer and its treatments had left their mark, Tobin was lucky in one sense. His learning and memory abilities were relatively unaffected. He and his mom got involved in the metformin trial, not so much to overcome these side effects, but out of curiosity to see what the team might discover and how it might help Tobin or other kids. And it wasn't their first time participating in research. Tobin had been part of Don's exercise trial, and both he and his mom had become ambassadors for SickKids to help raise money for research. Here's Tobin on why he got involved.

Tobin I think for me, it was a natural progression. And it feels good to give back. I think participating in research and individually, we can't really do too much, but collectively we do a lot.

Hannah For Tobin, participating in the trial meant taking metformin or a placebo daily for months and undergoing MRI brain scans and cognitive testing every few months to track his outcomes. But Tobin took it all in stride.

Tobin I do remember from the trial we would be asked a few times to come in for a whole long day of testing and scans and whatnot. I kind of enjoyed those days because I didn't have to do schoolwork.

Hannah After it was all over, just like the research team, Karen and Tobin awaited the results.

Karen I think I pestered the team. When are those going to be published and how quickly can this information spread?

Don So when I started the trial, I honestly didn't have any expectations. I thought, this is a great idea. Let's see what happens but I was skeptical. Because the history of clinical translation in neuroscience for drugs that work on the brain hasn't had a great track record because it's very hard to do. And because you can find something that works in an animal model but whether that can work in a human takes a lot of work. And many of these agents and drugs that have been identified in the past didn't actually have effects.

Hannah Would all their years of hard work pay off? It was a big gamble. But the day came when it was time to review the results. Don was looking to see if there was a difference between the results for kids in the metformin arm of the trial and the kids in the placebo arm.

Don If we saw a significant change in memory in the metformin condition compared to the placebo condition, that would be evidence that there is a signal there. I remember sitting in my office, ran the stats basically, does memory get better in the metformin group compared to the healthy group? And the first time I read it and I was like, Oh, it gets better. I'm like, OK, blink a bit and say, OK, let's do that again. And it's not like, it's like, Eureka, I found it because it's a small sample. It's a lot of variability. But there was something there, right? Then when my colleague Cindi Morshead showed me her data from the mouse

study and she was like, look at it Don, the mice who are treated with metformin, their memory is getting better and actually it's acting on the stem cells in the hippocampus. Like, there's something there. So I was excited. And I went home, told my family, I'm like, I think we're on to something. I don't know about your family. My family keeps me grounded and they're like, Oh, okay, great. Well, tell us when, tell us when you know when you know you found something.

Hannah The next step was to publish, to have peers review their work and let the broader community know what they had found.

Don We wrote the trial up. I was very excited about it kind of shot for the moon for very high impact journals. And we got shot down.

Hannah Don thought he might have more success with a smaller journal, but a colleague encouraged him to keep aiming high to see if a slightly different approach might help him break through.

Don She's like, no Don, this is an important story. And maybe if you kind of bundle it together with something else and then it made me think of Cindi's mouse studies, and we realized these are two parallel, analogous metformin clinical trials. One in mice and one in humans.

Hannah Don and Cindi decided to combine their studies into a single paper.

Don The only way we could do that was because from the very beginning, we planned these parallel studies.

Hannah The paper was accepted by Nature Medicine, a high impact journal, and was published in July 2020.

Don I remember I was at home. It was during the first lockdown, actually, that I found that was published. And suddenly my family heard me screaming and yelling because I got the email that we were it was accepted. Then they're like, what's going on?

Act Five: The Big Question

Hannah We could stop the story there with the team's breakthrough publication. But the truth is, it's just the beginning.

Don We have a signal. Now we have to see if it's real or not.

Hannah The team was fortunate to secure a multi-million dollar grant to run a large clinical trial across 15 sites in North America and Australia.

Don Now we're looking at the same things that we did in the first trial. Does it help the hippocampus to grow? Does it help memory? Does it help information processing speed? But now when we're done, we'll be able to say definitively, does this really work or not? And if it does, then we can start saying, OK, how do we now change practice?

Hannah This next trial isn't just larger and more powerful with the potential to answer the big question: can we heal the brain? It's got something else going for it. Karen and Tobin are now official members of the research team.

Don I'm an expert, but I'm not an expert in the lived experience of a family, of having a child with a brain tumour, right? And so I need to hear from those individuals. I've known Karen and Tobin for years. I think Tobin has participated in every research study I've ever conducted. And when I talked about, you know, I can count on one hand, the number of kids have gone on to university. Tobin is one of those kids. He has gone through as much or more than any kid in terms of his brain tumour treatment and diagnosis. But he went on to University of Calgary and is completing a degree in nursing. So when we developed the latest clinical trial, Karen and Tobin were part of the team who helped us write the grant. And they both had really important feedback on how we are going to conduct the metformin trial. What's the best way to approach families? What's going to overwhelm families? All of these things.

Karen There are so many things that I've learned about research over the past few years. And I know there's still a lot more to learn, but to simplify how I explain the patient and family involvement in research is, it simply makes it better because families and patients ask different questions. And we have the lived experience of the burden of time or the burden of you know taking medication.

Hannah The big trial is just getting started, and we won't know the results for a few years. But I asked Freda, Don, Karen and Tobin what it means to them.

Freda We're really excited because currently we have nothing for brain repair. Nothing. Even something that gives us 10 percent improvement, is a huge win. Metformin falls within the category of things that will help but will not take someone from having a giant brain injury to completely bringing them back to normal. So that's a really important point that I really want people to understand. We are not taking people who are, for example, paralyzed in a wheelchair and bringing them back to what they were. We are, though, hopefully going to be if this all works out in the end, providing them the ability to do something a bit better than they could do before, which is, if you're that person, is a huge improvement.

Don One of the parents said this is the first time I have hope that we can actually make a change. So I think it gives lots of hope. We have to be careful with that hope because we don't want to oversell because we still don't know. But I think there is that hope is different than before.

Karen It's really exciting to know that from that initial idea that Dr. Mabbott and team had that this already available medication could potentially help kids like Tobin. I know that research, it can seem really slow, but to know that now there's this knowledge and it's spreading and with this trial, it will continue to be used as it shows efficacy.

Tobin I think just the effects of cancer treatment, I think it's so detrimental. It's hard to see these kids suffering and going through this and the effects that it has on their families and their communities, and their friends. But I think now having this one drug that has potential new implications of how to improve the quality of life long term, maybe reduce those side effects for brain tumour patients is phenomenal. It's great. And it could also help countless other patients.

Hannah Tobin's right. If the clinical trial shows that metformin can heal the brain, it will open the door to help countless other patients and not just brain tumour patients, but also potentially kids with cerebral palsy, multiple sclerosis and other conditions where the brain

is injured or degenerating. Don and Freda are already working to expand the application of metformin by launching new studies with new partners and new patient populations. And they're starting to ask: what else might repair the brain and how might those agents work alongside exercise and metformin to have an even bigger impact for kids? They're continuing to ask big questions because their work isn't finished. But to bring our story to a close, I want to go back to the beginning. I asked Don if he had the chance, what would he say to the father who challenged him all those years ago to do more?

Don If I was talking to him, I'd say thank you for inspiring me. It's still not enough, but we're moving in the right direction. It's not enough until we get to the point where treating a brain tumour doesn't leave kids with these devastating learning issues. All the parents that I've worked with have motivated me in some way or another, either it being very directly like that father or just questions that I would get from families, well what can I do? How can I help my child? And every parent asked me that question. And now I think we have a better answer.

Hannah From SickKids Foundation, this is SickKids VS. Thanks for listening. If you want to support work like this, visit [SickKidsFoundation.com/podcast](https://www.sickkidsfoundation.com/podcast) to donate. And if you like this podcast, please subscribe and rate us on Apple or Google Podcasts, Spotify or wherever you listen to SickKids VS. SickKids VS is produced by me, Hannah Bank, Neil Parmar, Jasmine Budak and Gillian Savigny. This episode was written by Gillian Savigny. Sound Design and Editing by Quill. Production Support by Ayesha Barmania. For behind the scenes extras and show notes visit [SickKidsFoundation.com/podcast](https://www.sickkidsfoundation.com/podcast).