Hypermutant Tumours

Hannah: It's the spring of 2014 in Quebec City. Oncologist, Dr. Valerie Larouche, sees a new patient—a three-year-old boy with a brain tumour. (To protect the family's privacy, we'll call him Jacob.) By the time he's referred to her, Jacob's already had brain surgery to remove as much of the tumour as possible. Valerie starts him on radiation. Half a year later, Jacob's six-year-old sister comes in. (We'll call her Sofia.) She's got a splitting headache and has been throwing up. She is also diagnosed with a brain tumour and has brain surgery to remove the growing mass. Valerie starts her on radiation, too. In both kids, the cancer is moving quickly. The treatments aren't working. And they're running out of options. Valerie knows something is very wrong, but she doesn't know what. She's never seen siblings with such similar cancers at the same time. She reaches out to two doctors—her former mentor from SickKids, and his colleague. The symptoms sound like something they've been researching: a super aggressive cancer syndrome.

[MUSIC]

INTRO:
Welcome 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 Hypermutant Tumours.

ACT ONE

Dr. Tabori: My name is Uri Tabori. I'm a physician here at The Hospital for Sick Children and I treat kids with cancer. I also do research, which we call translational research, hopefully to find new approaches how to treat these kids with cancer.

Hannah: That's one of the doctors Valerie calls. And this is her past mentor.

Dr. Bouffet: My name is Eric Bouffet; I am a paediatric oncologist. I have been at SickKids for nearly 20 years. My job is to look after children with brain tumour.

Hannah: Eric and Uri have offices across the hallway. They work closely together, and they're good friends. Eric is French. Uri is Israeli. Eric was once Uri's mentor, too. Now Eric wakes up to ten emails from him each morning. But he doesn't seem to mind.

Dr. Bouffet: It's really a pleasure to see him on a daily basis and when he's not here I'm looking for him.

Hannah: In 2003, over a decade before they get the call from Valerie, doctors in Jordan and Pakistan reach out to SickKids through a monthly teleconference where doctors discuss hard-to-treat patients. They present a terrifying phenomenon: children with not just one tumour, but two or three, or even more. And they're dying quickly.

Eric and Uri start gathering samples of the tumours. Testing shows these patients have a syndrome called biallelic mismatch repair deficiency. We'll call it mismatch repair deficiency for short. First discovered in 1999, mismatch repair deficiency is a predisposition to extremely aggressive cancers. By the time most kids with this syndrome are 10 years old, their bodies are riddled with tumours. And none survive into adulthood.

Eric and Uri form an international group to study the syndrome. It takes years before they figure out why these tumours are so hard to treat.

Dr. Tabori: Usually in children's tumours you have one or two mutations and that's enough to create the cancer. When we first looked at the genome of these patients, we didn't find one or two, we found two hundred thousand. So that's not once or twice more. It's thousand times bigger."

Hannah: They realize the tumours are hypermutant. In a healthy person DNA is constantly repaired as cells divide and replicate. In these kids, cells can't fix mistakes during this process. This genetic mutation causes a rapid wave of cancer. One researcher dubs it the "great flood." [1]

[1] http://www.sickkids.ca/AboutSickKids/Newsroom/Past-News/2015/Study-identifies-highest-mutation-load-in-any-human-cancer.html

ACT TWO

Hannah: Eric and Uri get the call from Valerie. She's terrified for Jacob and Sofia.

Dr. Bouffet: One day, out of the blue, we had an email and a phone call from a colleague from Quebec who say, "I need your help. I have seen your paper, I have a child with a recurrent tumour, has been treated with a standard treatment, and now the tumour is back and I don't know what to do."

Hannah: Suddenly, all of Eric and Uri's knowledge needs to be put into practice. And fast.

Valerie sends tissue samples to SickKids. The team confirms the tumours are hypermutant. Both kids have mismatch repair deficiency.

Now Valerie knows it's this aggressive, highly deadly cancer syndrome. And she knows that the standard treatment—chemo, radiation, and surgery—won't work. But what she doesn't know is that the very thing that makes this syndrome so deadly, might also be its greatest weakness.

Dr. Tabori: We were trained to think that many mutations is bad, isn't it? But actually it can be good for us, bad for the tumour. So when a tumour has 10 mutations it's probably worse than one. But when it has two hundred thousand it's actually [an] inefficient tumour. So, [with] many mutations the tumour is less efficient and actually is exposed to the immune system, because the immune system can look at the tumour and say, "Oh, this cell with a lot of mutations is a bad cell, I want to attack it."

Hannah: But the immune system *isn't* attacking them. That's because our body's tissues have multiple immune checkpoints, a biological verification system which is designed to prevent the immune system from attacking healthy cells. Not only do the bad cells need to *look* bad, they need to signal that they're bad, too. But the hypermutant tumours aren't doing that. They're smart; they keep quiet. Which is why the immune system won't attack. It's stuck at this checkpoint.

But if Eric and Uri can bypass the immune checkpoint, they can unleash the full power of the immune system to attack the cancer. And they think they have a new group of drugs that can do just that: immune checkpoint inhibitors.

The only problem is that the drug isn't approved for kids. But, there's a loophole. If a patient has a life-threatening illness, the drug company may offer the medication on a compassionate basis. Because Sofia is so sick, they get the green light to try the checkpoint inhibitors. But what happens next is not what the doctors expect.

Dr. Bouffet: One week after she received the dose, we heard from our colleague physician in Quebec that she was not doing well. She was having repeated seizures, she was admitted in ICU, it was just a nightmare and we thought this was a disaster. And she had the repeat scan that was showing not only that the tumour had grown locally, but there were a lot of other tumours. It was like her brain was like a Christmas tree.

Hannah: But the family wants to keep going with the treatment. And so does Valerie.

Sofia starts to get better. Then Jacob starts the checkpoint inhibitors. Like Sofia, the first dose lands him in the hospital with scary seizures. But then he improves. Things seem to be going well. Until Sofia's treatment stops working.

Dr. Larouche: After that she had had a very good quality of life for a few months.

Hannah: In cancer care, quality of life is an important consideration for doctors. They know they might not be able to save every patient's life, but ideally they can give kids like Sofia the chance to be kids a little longer.

Dr. Larouche: She was attending school and doing activities but unfortunately, she has another deterioration. Nine months later with significant headaches and progressive disease. And then she passed away.

Hannah: The family is devastated. Even more terrifying, their son is still fighting for his life.

The medical team and the family regroup.

They add another drug to fire up the immune system. And then, they wait.

Every three months, they do an MRI to see if Jacob's tumour is shrinking or growing. In the summer of 2016, the MRI shows something shocking. The tumour is gone.

Dr. Larouche: When they come through the MRI, they come at the clinic and we look at the image and compare it to the previous one, it was amazing because we couldn't see any residual tumour. So we were happy. Mom and dad were crying.

Dr. Tabori: This is was the first time in several years which I just sat down at home and cried. Because as doctors we never get used to that—but we see more and more sad stories and we learn how to deal with them. But I've never heard about the brain tumour that disappears and once I heard that, I couldn't tolerate that. It was a happiness cry but it was something that didn't happen me for years.

Dr. Bouffet: It was so emotional. It was really one of these moments where you say, "Okay, it was worth it."

ACT THREE

Hannah: Now there's an international clinical trial for these hypermutant tumours using checkpoint inhibitors. It's in four countries but the hope is that it'll expand to 18 centres across the world. More than 50 patients have been treated so far.

But this research isn't just helping kids with rare cancers. It has implications for more common cancers, too, in both kids and adults.

Dr. Tabori: So what happened when we published this paper on 80,000 tumours actually, what happened is that suddenly a doctor that has a patient with prostate cancer that nobody will think that it can be hyper mutant, will do the right sequencing and can put the patient on immunotherapy. A patient with breast cancer, a patient with multiple others. So that's the beauty, when you share that information and you make sure that it's done the right way, then other people around the world can use the same intelligence or knowledge to treat cancers which have nothing to do with our syndrome. So it is the beauty of the world today.

Hannah: Checkpoint inhibitors are just one example of a new wave of treatments called immunotherapy, which harnesses the body's own immune to fight cancer. Dr. Jim Whitlock, the Director of the Garron Family Cancer Centre here at SickKids, considers it revolutionary.

Dr. Whitlock: And I can imagine a day, probably after I'm retired but I hope that I'll still be able to see, where immunotherapy for many children replaces the poisons of chemotherapy and allows children to have treatment that's not only more effective, but has many fewer short term and long term side effects.

Hannah: Three decades ago, most kids didn't survive their cancer. Now, more than 80 percent will. That's because of this kind of research. Because of collaboration. Because of immunotherapy. Because cancer leaders like Uri and Eric and their team are relentless in their search for answers. Because SickKids brings together great minds from around the world. But the fight is far from over.

Hannah: Jacob finishes his final immunotherapy treatment. He's a kid again—back at school, playing soccer with his friends. Three years later, in November 2019, a routine MRI finds another tumour, this time in a different part of his brain.

The diagnosis is a setback and scary for the family – but it's not hopeless. Like I explained in the beginning, kids with mismatch repair syndrome can get multiple tumours throughout their lives. This new tumour is not a relapse – it's just the nature of the syndrome. Which means the immunotherapy worked on Jacob's first tumour. And Eric and Uri think it might work even *better* now because they're treating the new tumour right away.

Dr. Bouffet: This is a discipline where you fight every day; you fight for life. And to me this is a privilege to do this and this fight is really the driver of my life. I'm born like this: I'm a competitor, I'm a runner, I'm a cyclist, I'm a fighter.

Dr. Tabori: I will have to cite. "You can't always get what you want, but if you try sometimes you'll find, you'll get what you need." So the issue is not to do things which are impossible. It is to keep on trying, and you will be surprised what things you can achieve. So I will fail and I'm failing on a daily basis, but it's

not the issue. The issue is to try to find new things and sometimes you'll get successes. And the second one is, "and in the end the love you take is equal to the love you make," that's actually a Beatles song. And it's all about that because when you give, you'll get back. Without that you'll never get back. So it does work. No, it's not exactly what you planned or what you wanted, but things, good things happen all the time.

EXTRO

Hannah: From SickKids Foundation, this is SickKids VS. Thanks for listening.

If you want to support work like this, visit sickkidsfoundation.com/podcast to donate. And if you like this podcast, please subscribe and rate us on Apple podcasts, Spotify, or wherever you listen to SickKids VS. SickKids VS is produced by me, Hannah Bank, Kate Daley, Colin J. Fleming, and Gillian Savigny.

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