Season 1 –Episode 10 –Dr. Michael Hoffman
Transcript

CHRISTIAN COTÉ
Welcome to Behind the breakthrough the podcast all about groundbreaking medical research and the people behind it at Toronto's University Health Network Canada's largest research and teaching hospital. I'm your host Christian Cote joining us on the podcast today. Dr. Michael Hoffman an award-winning scientist that you chance Princess Margaret Cancer Centre he's pioneering our understanding of how and why cancer starts. He'll join us in a minute. But first here's the backstory on Dr. Michael Hoffman.

Growing up in Austin Texas one of Michael's early memories is in the early days of home computing in the '80s. At age four he remembers watching his dad a computer programmer at the keyboard. Michael watched long enough to figure out his dad's password and then, when no one was looking, he'd log on to mimic his father's inputting. By age 6 Michael had his own computer and at 10 was going to computer camp. He loved to get programming books and retype the programs into his computer to create games.

It was like magic he says making a book come to life and watching a computer take on a life of its own. At university he majored in biology the study of life and went on to apply his computer skills in the emerging field of computational biology, where he now gathers millions of pieces of data and writes his own programs all in an effort to determine how cancer get started in the body with the goal of being able to predict when and where cancer begins so that it can be stopped before it ever starts.

Dr. Michael Hoffman, scientist at UHN's Princess Margaret Cancer Center, welcome to Behind the Breakthrough.

DR. MICHAEL HOFFMAN
Thanks for having me.

CHRISTIAN COTÉ
We should start with what is a computational biologist?

DR. MICHAEL HOFFMAN
That's a good question. So, a computational biologist is just a biologist who uses computers to figure things out about biology. That is my primary tool. Some people use a microscope. Other people use little equipment that moves liquids from one dish to another. I use a computer. And I manage a lab of other researchers and we all use computers to figure things out about biology.

CHRISTIAN COTÉ
So, let's step back for a second, big picture, what do we know about how cancer get started?

DR. MICHAEL HOFFMAN
Cancer is a disease of the DNA. So, your cells all have roughly the same DNA, but you have many different kinds of cells. The DNA acts as a program for your cells and tells them what to do, and in different kinds of cells such as muscle cells versus brain cells versus skin cells, different parts of the program are run. What happens in cancer is that the wrong program gets run. Certain parts of the DNA that tell these cells to stop dividing get turned off, right? The wrong program runs and the cells divide in an unrestricted manner, and there are a bunch of other things that happen and you end up with cancer. Basically all of these little defenses that are part of the normal programming of your cells go awry.

CHRISTIAN COTÉ
So if I have this right your research is looking into finding those genes that have gone awry? And then once you do find them, you look for the source of what made them go awry, those switches that have turned the genes off or on when they're basically not supposed to?

DR. MICHAEL HOFFMAN
Yeah that's about right. So there are about 20, 000 protein coding genes in the human genome and they cover a small proportion of the genome and much of the rest of it functions to enable these gene expression programs, to enable the program of certain genes being turned on or off at certain times and places and environments. And so there can either be changes in the DNA itself, mutations that can result in the wrong gene expression program being run, and there can also be influences from the environment that will result in the wrong gene expression program being run.

CHRISTIAN COTÉ
Okay so let's dive into your work Michael, how do you search for genes gone awry and the switches that trigger them by using data?

DR. MICHAEL HOFFMAN
You might have heard about high throughput DNA sequencing?

CHRISTIAN COTÉ
No.

DR. MICHAEL HOFFMAN
No. Have you heard of Next Generation Sequencing?

CHRISTIAN COTÉ
Treat me as if I'm in Grade 5, Michael.

DR. MICHAEL HOFFMAN
So, people have these machines that can sequence DNA and by sequence it really just means reading out the order of A,C,G, and T. DNA is a polymer. All right. Much like now nylon or

something. Right so it's made up of a lot of individual repeating units span like say nylon where every unit is exactly the same. And DNA, there are four basic kinds of units. So we refer to these by their first letters. So there's "A" for Adenine, "C" for Cytosine, "G" for Guanine and "T" for Thymine, and that's what the program of the genome is actually written in is these letters.

So you know if you were going to sequence the letters on a piece of paper that would mean getting the letters out in order or in sequence as opposed to just getting a whole jumble of letters which you know doesn't really help you to know that a piece of paper has say more E's or than O's for example. So these machines can sequence a lot of DNA and and the last let's say 15 years or so people have developed DNA sequencing machines that work much faster than the ones that were used for the Human Genome Project. There was a draft human genome sequence that was finished I think in 2001 and that was the the culmination of 15 years of focused work and more preparatory work going back decades earlier. So, it was only then that we had something even approximating a full sequence of the human genome, the three billion A's C's G's and T's that define this program that exists in every one of your cells. You know it took years and years to generate the draft human genome sequence and now there are labs all over the world that are generating DNA sequence that are multiple of the human genome every day. So, so much data coming in. So, some people are excited about all this high throughput DNA sequencing because they can use it to find lots of genetic variation. So while the DNA program is mainly this team from person to person there are little changes, right?

So, there are little changes that might lead to someone having brown eyes, someone else having red hair. These are usually sorts of things that are caused by by little DNA mutations. Right. But they are a small proportion of the genome the reason I'm excited about this new DNA sequencing technology is because you can use it as an instrument to figure out things about physical and chemical properties of the genome. So, if you remember we were talking about how the cells all have roughly the same DNA right, but they're different kinds of cells. The way the cells know what kind of cells they are are basically bookmarks or other signals that are on top of the level of the DNA. So there might be a particular gene that's turned on to cause something to become a muscle or that causes it to become liver. So, the sequence remains the same but there are things, like there are other molecules that are nearby the DNA and that will change from one cell type to another with any particular human. So, these high throughput DNA sequencing technologies what they allow us to do is set up experiments so that we can figure out where these different signals are, right? So, you can setup an experiment that will say look for what we call open Chromatin. All right. So, you have about two metres of DNA in each cell but its compacted into something that's you know much smaller than that. Yeah, dot of an eye.

CHRISTIAN COTÉ
And what's chromatin?

DR. MICHAEL HOFFMAN
Chromatin is what we call the DNA chromosomes and all of these other molecules that are associated with it. So it's kind of like a dance of this DNA and there are literally thousands of

different types of proteins that interact with it. Right. And depending on where those proteins are, determines what kind of cell type you're using.

CHRISTIAN COTÉ
As a computational biologist you spend a lot of time analyzing, interpreting data, that data I imagine is telling you something, a story. Have you got a sense of what the story is that you're reading at this point?

DR. MICHAEL HOFFMAN
So, the story is basically that there's a really complicated set of machinery that tells genes when to turn on and when to turn off and we're trying to figure out how that machinery works and whether we can predict which genes will be turned on and off say given the state of the machinery or ideally given changes in the DNA or given different changes that occur in the environment. For a long time this sort of thing was treated as a black box problem. So you have a black box, in goes the DNA and goes environmental conditions and out comes a certain gene expression program, some genes being turned on some genes being turned off. Well we have now more is what some people call a grey box. We don't really understand completely how the machinery works but we can see inside of it we can see this state of various bits of the machinery and we're trying to understand that better and by collecting a lot of data on what the machinery looks like in different sorts of cell types and different kinds of conditions and developing new computational tools that help us identify patterns within these states we hope to discover how this program works.

CHRISTIAN COTÉ
I understand you've discovered patterns with regards to these genes and switches, correct?

DR. MICHAEL HOFFMAN
Yes, we can read out a lot of information about essentially a very small neighborhood of DNA. And so if we went to sort of Google Maps type example for this we already have the base map from the Human Genome Project and let's say we send a drone out and the drone can give us facts and figures about individual addresses. Right. So it might be able to tell us that at this address the building is this high. And at this address the building is made of brick. And at this address the building has this many windows and so on. So, you get all of these individual pieces of information in what we call tracks. So, there are individual tracks of data. Each one tells you something about some property of the genome at some position and then you can discover patterns that occur across multiple tracks. So, you might discover that there's a recurring pattern of buildings that are 60 stories tall and made of glass and that have certain kind of shops on the ground floor. All right. And even if you didn't know anything about the way Toronto worked you might find this pattern and then investigate it further and then realize that you have discovered the condo building. Right. Or other sorts of patterns might have to do with churches or stores or parking lots or things like that. Right.

Any of these types of locations or things that will have individual patterns in all of these different sorts of tracks of data that we're looking at. And there are a couple of ways of using a computer to

find them. Either you can do this in unsupervised way where you just throw all the data at the computer and say tell us which patterns we see over and over and over again right. Or you can do it in a supervised way which is for example you're trying to find all of the Shoppers Drug Marts. Right. So, you tell your computer what a Shoppers Drug Mart looks like and you give it say a few examples of Shoppers Drug Marts and then you train the computer and then you let it work on a lot of other data which you haven't labeled manually and it picks out all the Shoppers Drug Marts for you.

CHRISTIAN COTÉ
So, if I was to swap out Shoppers Drug Mart and certain cancer there is there anything we know yet about the pattern for why a cancer cell starts?

DR. MICHAEL HOFFMAN
There are particular sorts of genes that go awry frequently in particular sorts of cancers. Perhaps the best understood cancer in this regard is breast cancer. There are hormone receptors that play a big role in breast cancer. So, for example estrogen receptor right or progesterone receptor or something called HER2, which is a different growth factor that is a signal that you have a particular sort of cancer and this sort of information is actually used by people at Princess Margaret Cancer Center to help decide on what sort of drugs people should get.

So, in addition to estrogen and progesterone, I mentioned there is a receptor called HER2. So, people with HER2 kind of cancer are prescribed something called herceptin. All right. The HER is the same there. And the clinicians use this information to decide that people should get that drug instead of some other drug because now, you know we don't just see people come in and have breast cancer, we are often able to figure out the molecular cause of their breast cancer or other kinds of cancer. As I mentioned at the beginning, cancer is a disease of the DNA. It's not a disease of a particular organ type, yes you know if you have leukemia or liver cancer or breast cancer there are often particular genes that are involved in those sorts of cancers. But at the end of the day it's something that's going on in individual cells that have developed cancer and that's what we try to figure out.

CHRISTIAN COTÉ
That's amazing in terms of being able to identify that in breast cancer, in terms of other cancers, presumably you're going down the road of trying to find which switches or what telltale signs there are with other cancers where are you at with trying to map that?

DR. MICHAEL HOFFMAN
In my lab we work a lot on leukemia. Leukemia is a horrible disease and often leukemia is curable, but sometimes you know there are cases where it is not. And so trying to understand what separates the treatable versus untreatable cases of leukemia is a really big deal. One thing that happens leukemia is there are a couple of genes that are often mutated in leukemia.

So, these genes are going awry and they are related to turning on DNA methylation. Right. So, there might be a gene that causes cancer that you want to be turned off. And if you mess up the

machinery that turns these genes off then you're in trouble. So, one of the things we're studying is whether this other class of proteins called transcription factors. We are studying whether and how they can recognize DNA methylation themselves. People in the past usually thought of transcription factors as recognizing individual codes of BCG and T. But there are more and more cases of people showing the individual transcription factors can also recognize an additional layer of information which is whether DNA is methylated or not.

CHRISTIAN COTÉ
So, where is this headed?

DR. MICHAEL HOFFMAN
The end goal of my lab and a number of other labs that work in similar areas is to be able to predict what sort of changes in gene expression per gram you get from upstream either changes in environment or changes in DNA sequence. So, this is important for two reasons. One it lets us do a better job of detecting when things have gone awry predicting disease diagnosis giving people prognosis that sort of thing. The other reason it's important is because it gives us an understanding of what within the cell is actually turning the cancer pathways on. Only when you have that understanding are you able to rationally design some sort of drug or other therapy to attack that. And in the future this is very much in its infancy today.

But I think you're going to see more gene therapy where clinicians will actually try to change people's DNA directly to directly fix things that are causing cancer or other diseases rather than introducing small molecules that they hope will interact preferentially with cancer cells.

CHRISTIAN COTÉ
I'm curious how much the advances in technology computing plays into or influences the work you can do or even shapes your research potentially?

DR. MICHAEL HOFFMAN
Yeah. Advances in technology definitely shape my research. I think the biggest advance is M Ps high throughput DNA sequencing machines. So, much of what I do now relies on data for these machines which you could have done these sorts of experiments maybe 20 years ago but it would have cost so much money that would be unfathomable it would not be practical. All right so this sort of technology allows us whole classes of research that we wouldn't have been able to do before. And in terms of computing we're able to do a lot more things more quickly. So, this sort of machine learning technique I talked about earlier we can do that a lot faster than we used to. We can try out different kinds of models more quickly and get to something that works more accurately. We can crunch more data at one point people would have had to reduce their data they would have had to predict in advance which columns of numbers were most important before trying to use it to predict something like what kind of cancer someone has.

Now that computers can and all of this data you don't have to do this sort of arbitrary data reduction and worry about potentially missing something and big picture.

CHRISTIAN COTÉ
What do you dream of your lab work leading to?

DR. MICHAEL HOFFMAN
There's a few things so, one is I want people to be able to do the sort of prediction I was talking about so I want people to be able to predict which genes will be turned on or off depending on what sort of environment or DNA change there is. So, this is something that people have wanted for a long time. And if that sort of ability ever comes out of the research of my lab and others it will really change a lot of other research and change our understanding of biology. One thing that's really important to me is training the next generation of scientists. So, in addition to being a scientist at Princess Margaret and at you Chen I am an assistant professor at the University of Toronto. So, I don't actually teach big undergraduate courses most of my teaching is through mentoring graduate students and undergraduates who do research in my wife? So, I want to teach them how to do research. Well how did you sound research how to do research ethically those sorts of things? Those are kind of my two biggest goals.

CHRISTIAN COTÉ
You're listening to behind the breakthrough a podcast about groundbreaking medical research and the people behind it at University Health Network in Toronto. Canada's largest teaching and research hospital. I'm your host Christian coach and we're speaking today with Dr. Michael Hoffman, scientist at UHN's Princess Margaret Cancer Centre. Michael you're Texas born and raised. You were doing postdoctoral work in Seattle. What on earth brought you up to Toronto?

DR. MICHAEL HOFFMAN
I would say mainly two things so there's kind of a virtuous cycle in terms of the sort of personnel you get if you have a team of really great people, more really great people are going to want to join that team. Right. Everyone wants to work with great people. Right. And so more and more people come here because of that. Toronto also has a lot of resources that a lot of other places don't have. Right. This is mainly because of the outstanding philanthropic community in Toronto that donate the money to make things like the Princess Margaret Cancer Center run. Without say people doing the ride to conquer cancer, I would not have the lights on in my lab. All right. So it's hard to do computational biology without electricity. We run on all of the people who have been bicycling or playing hockey to conquer cancer or all of the other really important philanthropic activities? The Princess Margaret Cancer Foundation runs. Another really interesting thing Toronto has is geography. So, we have such a concentration of world class institutions right next to each other near the corner of University Avenue and College Street. All right. You've got Princess Margaret. You've got Toronto General Hospital. You've got Mt. Sinai Hospital. You've got Sickids. You've got a lot of University of Toronto departments. And this just makes it so much easier to find colleagues to work with. To meet people to develop collaborations and that sort of thing. So there are other towns where there are several great research institutions and they're across town from each other and people basically never see each other. There's always a joke in each one of these towns about how you know they go to conferences on the other side of the world to see someone you know there's a 30 minute drive away, right. In Toronto, mostly, we don't have this issue.

CHRISTIAN COTÉ
I imagine failure is a part of research and I've heard a number of scientists say they embrace it. What's your take?

DR. MICHAEL HOFFMAN
You know I wouldn't say I embrace failure. It's just kind of a fact of doing research right. I'm I don't glorify failure. But people also shouldn't maybe glorify success too much right. Because often whether you end up in a failure condition or success condition is a result of luck. Basically the way you make your own luck is by doing a lot of different things. Right. So, if you work harder that's essentially more chances to roll the die and also learning as much as you can. So, if you learn what other people have done in the same area you can avoid doing the things that they've done. You can build on something they've done. And one of the things I do as a interdisciplinary researcher I kind of work between a lot of different areas, right.

So, I do genomics where I do machine learning I do cancer biology and often you can steal ideas from one of these areas and apply it to the other area. So, a lot of these pattern finding techniques that we use were originally developed for speech recognition. So, it turns out that doing things like finding vowels and consonants with an audio data is a similar problem in some way to finding these sorts of patterns with and genomic data and someone at the right time thought oh I can steal this approach that people have developed for years and years over here and apply it to this new problem and people have been developing that for years and years but that's often where some of the biggest advances come in is people taking knowledge from a field that isn't usually considered with their own field and bringing in them.

CHRISTIAN COTÉ
There's a quote by James Kabila, a data science analyst who says quote science is exploration; a journey that has no end. What you're looking for may never appear." It seems to underscore the fact that science takes time. So, do you ever find that frustrating?

DR. MICHAEL HOFFMAN
I mean it definitely takes time and it can definitely be frustrating. I think at earlier stages in one's career when you're say a grad student and you have one project going on it can be really frustrating to not make progress in that one project. But as people develop in their careers and feel more able to take on multiple projects and work on them simultaneously and maybe take on junior people that they mentor essentially they are improving their lock they have more irons in the fire they are more likely to experience success once you're running your own research group. Obviously there are a lot of different irons in the fire so it can affect you a little bit less. Plus you know people running research groups are usually capped extremely busy all right so you can't have too much time to think about how things aren't working.

CHRISTIAN COTÉ

You mentioned your satisfaction in terms of being able to mentor younger people in your life. So, give us a sense what's your approach to mentorship?

DR. MICHAEL HOFFMAN
In some ways being a research mentor is much more like being a coach than being a boss. I don't think you're ever going to get good results by cracking the whip and being like you weren't you weren't here 80 hours last week. What's wrong with you. Instead, you need to coach people and kind of help them figure out what their goals are and how you can help them achieve that. The motivation often has to come from within. I see you're quite active on Twitter.

CHRISTIAN COTÉ
Is this a platform that is can be useful for scientists?

DR. MICHAEL HOFFMAN
Yeah I found Twitter to be so amazing. I think I've been on Twitter for eleven years. Well you're an early adopter. I'm an early adopter and it has been so amazing for keeping in touch with colleagues. The analogy that I usually make is it's like a permanent hallway track. People talk about hallway track at a conference where you stand outside in the hallway and chat with your colleagues from maybe different institutions all over the world who maybe you've known for years maybe you just met right. This is a lot of how connections are made in science. And Twitter makes it much easier to keep up those connections. It provides a way where you can talk to people at any time about science and people who are interested in the kind of science you do might follow you and you'll have a lot of conversations about it? If you look at my tweets Most of them are replies and conversations with other people and this means I can keep up with people and what they're doing and what's going on their careers and what new science they're producing without say having to fly to a bunch of different conferences every year. So, it's extremely helpful.

CHRISTIAN COTÉ
You strike me as someone where this work that you do is all consuming. Does it ever turn off for you?

DR. MICHAEL HOFFMAN
It is hard for me to turn off and stop thinking about this stuff entirely. I don't want to say that I'm in the lab seven days a week because I'm not. I make a conscious effort to try to not do that. If you don't get one day off you eventually go a little bananas but you know at this level it's internally motivated. Mainly, it is a real privilege to be able to have this kind of job and to be able to use the newest technology to be able to learn things on a daily basis. To be able to learn things not just from other people but get to cheesier. Learn the secrets of the universe things that no one else knows yet and be able to teach people. So, be able to teach people the craft of computational biology to be able to teach other people what we've learned about biology or about early detection of cancer and it's all fine. You know it's a fun job.

CHRISTIAN COTÉ

Dr. Michael Hoffman scientists at UHN's Princess Margaret Cancer Centre. Thanks for speaking with us today and continued success.

DR. MICHAEL HOFFMAN
Thank you so much Christian.

CHRISTIAN COTÉ
For more on the podcast go to our Web site, www.behindthebreakthrough.ca and please let us know what you think, we crave feedback. That's a wrap for this episode of Behind The Breakthrough, the podcast all about groundbreaking medical research and the people behind it at University Health Network in Toronto. I'm your host Christian Coté, thanks for listening!