Season 1 – Episode 5 – Dr. Mathieu Lupien
Transcript

BTB
Welcome to Behind the Breakthrough, the podcast all about ground-breaking 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. Our guest today is Dr. Mathieu Lupien, senior scientist at UHN's Princess Margaret Cancer Centre. He's a pioneer in the exploration and understanding of the human genome and its role in causing cancer. He'll join us in a minute. But first, here's the backstory on Dr. Mathieu Lupien.

BTB
Growing up in St. Jerome, Quebec, in an all French household in the 1980s, Mathieu Lupien's heroes were scientists—people who made amazing discoveries such as Madame Curie, Louis Pasteur. By Grade 7, young Mathieu knows his passion in life is to study life, those organisms and elements that make up our bodies. So after high school, Mathieu chooses to study biology at the prestigious McGill University in Montreal, where classes, by the way, are conducted in English. Mathieu is undaunted by the fact he doesn't speak the language and decides he'll learn it at the same time he pursues his degree. In 1999, he graduates with a BSC, followed by a PhD in 2005. And then Dr. Lupien enters the research world to study the human genome and its connection to cancer. What gives cancer life in the body? How and where does it start? With the hope of one day stopping the disease from ever starting.

Dr. Mathieu Lupien, senior scientist at UHN's Princess Margaret Cancer Centre. Welcome to Behind the Breakthrough.

DR. MATHIEU LUPIEN
Thank you for having me.

BTB
Mathieu, how does cancer get started?

DR. MATHIEU LUPIEN
So cancer itself is a process where a cell can no longer differentiate, can no longer be, for instance, a skin cell or a muscle cell or something of that flavour. Instead what happens is that the processes that regulate the capacity of cells to differentiate are broken and there's multiple checkpoints. So you need to have multiple processes affected for a cell to lose its capacity to be normal and become a cancer cell. And then in the process, once all these checkpoints are broken, what happens is that the cell loses its identity. So a cancer cell is a cell that has lost its identity and often in the process what happens is that that cell starts dividing. So instead of only having one, you have two, you have four, you have eight, and so on and so forth. And that creates a mass because the cells are constantly dividing and dividing. Creates a mass that we call the tumour.

BTB
And what does that mass do?

DR. MATHIEU LUPIEN
So that mass then is going to be drawing in all the energy that it can, to be able to grow more and more because its concept is to grow. The ultimate concept of a tumour is to grow and grow and grow so it sucks in all the energy. So it will draw in blood, it will draw in blood vessels, it will draw in the energy that it can now in the same process. At one point you'll have the immune system that will come in to try to fight it off. And so it will learn ways to block the immune system. Find ways to hide from the immune system in order to keep proliferating and keep using up all the energy that it can from the host.

BTB
Now Mathieu, I want to do something a little different on the podcast today because I think to help me—and I think also our audience—understand your pioneering research. It's like we need a crash course in the human genome, if you don't mind. What is the human genome and what does it do?

DR. MATHIEU LUPIEN
All right. So the human genome you can see it a little bit more like an encyclopedia. The encyclopedia of what's required to make a human being. It's a gigantic book that contains over three billion letters and these letters will form words, sentences, paragraphs and likes to really provide all the information that's required to make a human being. As opposed to having an alphabet of 26 letters, the human genome consists of an alphabet of four letters. And that same encyclopedia is found in every single cell of your body. Every single cell of your body. Yet, you do have diversity in the shapes— like your ear does not look like your mouth and so on and so forth. And so the system has learned to use different parts of that encyclopedia to be able to make an ear, versus make a foot, versus make an eye, and so on and so forth.

BTB
So I guess you could say this is like a blueprint for the human body. I guess I'm still trying to figure out or understand—what's it made up of?

DR. MATHIEU LUPIEN
Right. So it's really like a book. It's really the equivalent of a book. It's a string of letters that are organized in specific orders that provide key words that our cells know how to interpret. They know that a certain string of letters implies that they're in that specific region of the encyclopedia that we call the human genome; there is all of the information that's required to make the key building blocks of a brain cell, like a neuron or a muscle cell.

BTB
And if you don't mind, indulge me a little further. DNA— what's that?

DR. MATHIEU LUPIEN
Right. So the DNA is the name we gave to the string of letters that make up the human genome.

BTB
So they're different from genes. How do they interact or influence genes?

DR. MATHIEU LUPIEN
So genes are individual units that are found within the human genome. Because we have to take into account this notion that, as I said, if we again keep up with this analogy of this encyclopedia, you need to have sentences, phrases, paragraphs and the like that are meaningful. And so within this, each sentence, you'll have all that you need—a noun, a verb, an adjective and so on and so forth. So a gene can be seen as a noun. It gives you a specific context, a specific identity, a specific item that you'll influence. That you'll either, say, let's have more of this one or let's have less of this one. And so a gene itself is a unit of the genome that I often refer to as a noun, which is there to encode for proteins. And proteins are an active form that is generated out of our DNA, that can actually engage in specific catalytic activity within the cell. So what that means is that a protein which comes up that says that is encoded by a gene more or less corresponds to a superhero in a book or something of that flavour that is engaged in an action shot. And so that protein will do something specific—will catalyze an activity that will ensure that your cell behaves the way it should be behaving.

BTB
So instead of creating a bone or some kind of muscle, it creates a liver?

DR. MATHIEU LUPIEN
For instance.

BTB
OK. I think I'm catching on. So I'm thinking also maybe a little history lesson might be useful here in terms of understanding how did we how do we know about the human genome. How did that come about?

DR. MATHIEU LUPIEN
So there was an international initiative to actually move forward in sequencing the human genome from start to end. Prior to that initiative we knew of individual genes being involved in the development of one disease versus another disease but we never had the full picture. And so at one point the scientific community—in alignment with politicians, actually, that supported this initiative—agreed to move forward and sequencing enough individuals to be able to have a clear sense of what's the reference human genome. Which is a reference, right. That's an encyclopedia, that's an average of what each and every single one of us would have in every single cell of our body. And so that was outstanding. That was a fabulous effort because in the process we learned a lot. We learned, for instance, that even though genes are often the focus of all that you hear in the public domain about scientific discoveries, genes are not all that there

is to be focusing on. Genes actually only account for about 1.5% of our human genome. And so that leaves 98.5% out there for which we had no clue of the function at the time. But if you think of it, would you be carrying around 98.5% of a book for no reason in your backpack? Not quite, right? So there's definitely a lot of functions that have been ascribed to that 98.5% of the genome but that came because we knew that it existed. Because we knew where to look in that, because we knew that we could interrogate that non-coding space.

BTB
So this is an important turning point. So I want to drill down a bit into this because what you've been talking about is the human genome project right? It was started back in the early 90s and this mapping of genes in our bodies, under the auspices of this project, took about, I don't know 12-13 years. It was in the early 2000s that it reported. So just take me back then to that time. What was the potential? What did researchers and scientists hope to do with this information of mapping the genome?

DR. MATHIEU LUPIEN
Well, so we knew that genes were important but we needed to identify how many more genes there were. Like, the concept was that we're a complex organism so we must be filled with genes if genes are so important. And yet at that time we had not yet identified what we thought was the sum of all genes. And so I think that there was a strong push at that time to sequence the human genome with the hope of being able to identify the sum of all genes. So at one point people expected that we would have over 100,000 genes in our genome, 50,000 genes. Like big numbers. It turns out that it's closer to 20-26,000 genes that we haven't done. And so that effort was definitely initially geared towards, I think, making a better map of all the genes that are out there. Because we were so gene-centric in our way of thinking that we needed to find all genes. In the process, we discovered a whole lot more.

BTB
And what was the promise back then, Mathieu, if you don't mind. I want to come back this again because it might help us understand why it's so important. What could it tell us or what was it going to do in terms of furthering research for the people who are working on the project?

DR. MATHIEU LUPIEN
All right. So at that time, for sure, genes had been clearly established as key of key elements disrupted in disease. So we knew for instance that if you had a mutation in a given gene you were likely to have a cancer or likely to have Huntington, or likely to have another disease. Like genetically inherited diseases—those diseases that individuals passed down from generation to generation or that inherited from their parents.

There was a strong bias back in the 90s that those were driven by genes that mutations and genes would be key determining factors in the likelihood of developing a given disease. There were a lot of evidence supporting that notion. And so the concept was, let's find all the genes and this way we can find all the genetic causes of disease.

BTB
Terrific. So, I found it curious when I was doing research preparing for our chat today, that it seems almost as soon as the human genome project wrapped up in the early 2000s, as soon as it presented its findings. It seems almost immediately that researchers realized—and you've hinted at this—that while helpful in advancing the field of gene study and how that governs the human body, that genes are actually only a small fraction of the human genome. Only 1.5% as you pointed out. So what happened there? Why was that 98.5% of the rest of our genome left uncharted?

DR. MATHIEU LUPIEN
Right. So I'll actually also use that example just before I answer your question to showcase a fundamental aspect of research. We initiate our research with a clear hypothesis, with a clear expectation, but that expectation is not necessarily met. But it doesn't mean we're not going to discover something. We still manage to discover something and it opens up our mind to an alternative interpretation of the data. And that's critical. That's a critical concept within the scientific endeavor. We formulate hypotheses and we move forward with them because we see that they are supported with the existing evidence. But then in the process, if we find something different we're not going to say 'No, that's not the case.' We're going to observe it and we're going to acknowledge it and we're going to work with it. And so when the human genome sequencing was completed and it was then released that, look, there's only 1.5% of our genome that encodes for genes that can give rise to proteins and the like. We're like, all right, well, now there's this 98.5% that's left. Clearly that has to be something to do with that 98.5%. And so that launched a completely new initiative to better understand exactly what the role of that 98.5% was.

BTB
So, some, as you say, people begin that work of mapping the remaining 98.5% and to understand it better. Which is about the same time you're finishing your PHD at McGill in biology and actually at the time you're studying about genes. Tell us about that.

DR. MATHIEU LUPIEN
Right. So this is a, you know, this is following science right. So at the same time that the human genome was completed, that also allowed for a large number of new technologies to be developed. A number of new technologies actually geared to be able to understand the genome, regardless of whether we were looking at the non-coding or the coding space—like the genes or the non-gene space.

And so when I did the transition from completing my PHD at McGill University to then start a postdoctoral fellow at the Dana Farber Cancer Institute, affiliated with Harvard University, I actually had the chance to tap into these emerging technologies. And even though at the time the studies that we were focusing on were looking at genes still, our mind frame had switched. We weren't anymore looking at the genes themselves and trying to figure out if there's mutations in them that could contribute to cancer—because at the time I was working on

breast cancer. What we started doing was like, ok, we have these genes that we know are contributing to breast cancer development but so how is it that their expression is regulated? So how is it that the cells know how much of it to use to give rise to proteins and that's what led us into looking at the non-coding space. Because what we discovered in the process is that that non-coding space was filled with individual functional units that were critical to regulate how much of a gene a cell uses. So if you want an analogy for this, if you think of a gene, let's say, as a light bulb—I like to use it as a light bulb. Now, if you turn it on, it creates light. So light will would be the equivalent of a gene being expressed to give rise to a protein. Now, turning it on is a process. It's a process that requires elements that are not the light bulb, right?

BTB
And they're not the gene?

DR. MATHIEU LUPIEN
And they're not the gene, right. If the gene is the light bulb, then whatever turns the light bulb on is not the gene. It's an element that's independent, per se, and design to the gene but that still plays a role in regulating how much of that gene will be expressed. How much of that light will be turned on. And so that can be seen, for instance, in our daily life as a light switch and a dimmer. So the light switch turns it on and the dimmer regulates how much of that light comes out from that light bulb. So it's the same principle for genes. For genes to be expressed you need to have a light switch that's turned on, and then you need to have a large number of dimmers that fine tune how much of it is being expressed. And all of these dimmers and light switches fall in the non-coding space.

BTB
That 98.5% wilderness that had not been charted by the human genome?

DR. MATHIEU LUPIEN
Exactly. It's not all of it. 98.5 is not just light switches and dimmers but depending on the estimates, right now we're around 20-40% of the non-coding space corresponding to switches and light dimmers.

BTB
You know what I find interesting at this time was the sort of transition from Human Genome Project to studying the 98.5% that had not been charted is—correct me if I'm wrong—there was some resistance?

DR. MATHIEU LUPIEN
Well, whenever you propose something new, which is again a fundamental concept within science—which is good—people will criticize it. But that's our daily job. We want to make sure that we identify the truth and to identify through the truth means coming up with a hypothesis, testing it, putting it forward and then allowing our peers to reassess our work to then also engage in their own studies to validate or disprove.

BTB
Can it be replicated?

DR. MATHIEU LUPIEN
Exactly. And if it's disproved, we're fine with it but then again we'll have to assess the extent to which it can be disproved.

BTB
This resistance though, is that what gave rise to kind of this sinister name of this 98.5% wilderness.

DR. MATHIEU LUPIEN
Right. So back in the early 2000s that 98.5% was referred to as junk DNA. And that was definitely a strong bias in its interpretation.

BTB
It was also called the dark genome?

DR. MATHIEU LUPIEN
So the dark genome is more recent, actually, because the dark genome has a positive connotation.. Because the dark matter and the likes—these are concepts that we agree exists. And so acknowledging that it exists is a big deal. But, yeah, definitely at first it was referred to as junk DNA. And junk, clearly that's not, that's pejorative. Right. It's not positive. But the dark matter, I'm okay with. Like, we're investigating, engaging, exploring the dark genome. I'm totally fine with that.

BTB
So I'm curious. Back in 2005, completing your PHD at Dana Farber at Harvard. What drew you then to studying this 98.5% where there was some kind of resistance actually from the scientific world in parts of it to go after it?

DR. MATHIEU LUPIEN
All right. So two aspects. First, technology was enabling us to actually study it very effectively. The second aspect, that was very engaging as well, was this notion that each cell in your body, again, has the same sequence. Like the human genome is different between me and you. But within each of us the human genome is more or less relatively the same across all the cells that make up our body. But yet, again, they don't look the same. A neuron does not look like a muscle cell does not look like… right. Your foot does not look like your hands or whatever else.

BTB
Thank goodness.

DR. MATHIEU LUPIEN

Yeah. So I was puzzled by this notion. But not in a normal development concept, but more in a disease concept. So again there in cancer, for instance, we have some specific genes which we know are oncogenes. So drivers of transformation, drivers of cancer development. And sometimes the exact same oncogene is—

BTB
Sorry, Uncle Gene?

DR. MATHIEU LUPIEN
Oncogene.

BTB
Oh I see, in terms of oncology.

DR. MATHIEU LUPIEN
Exactly. A gene that promotes cancer. So we can call them oncogenes. And so those are genes that are not necessarily different. Like, they're the same genes often that are used for normal development. It's just that their regulation or their function is altered and to promote cancer development. And so at the time I was puzzled by the fact that the same oncogene could be involved in different cancer types and yet these different cancer types were not at all identical. They were completely different. And so I had to figure out why an oncogene would work in a certain way in one cancer cell and in a different way in a cancer cell from a different tissue of origin.

BTB
So let's go further here. What have you discovered then in this dark genome— if you want, if we're gonna call it that now—that you know goes on in your lab? What are you discovering?

DR. MATHIEU LUPIEN
Right. So there's multiple aspects. So, one of the most critical discoveries that we made…around 2008, 2009, was this notion that, yes, you could have an oncogene giving rise to a protein that actually would behave differently in one cancer type versus another. And the reason we could account for these differences were based on what I call the readability of the human genome.

BTB
The readability?

DR. MATHIEU LUPIEN
The readability of the human genome. So we talked about light switches and dimmers. So even though you have light switches and dimmers that are at specific locations in the human genome again they're not all used in all cell types. So a subset of them will be used in one cell type. Another subset will be used in a different cell type. And it was always a challenge to be able to figure out exactly which ones are used in cell type 2 versus which ones are used in cell type 2.

And so in 2008, approximately, we started looking at an additional layer of information that's provided on the human genome, which refers to the concept of epigenetics.

So epigenetics is more or less the process of bookmarking the human genome—telling the system which light switches should be used. Telling the system which genes should be differentially expressed. Telling the system which dimmers should be used. And so we started characterizing these bookmarks that are coming out from the process of epigenetics. If you want an analogy, for instance, the human genome—I referred to it as an encyclopedia in the past—you can also visualize it as the map of all roads and cities that we have for our planet, our country—whatever scale you want to use.

While we know where the cities are, while we know where the roads are—which is the equivalent of having the human genome—if you want to make your ways from one city to another, maps are useful but if you can have guidance, right? If you can have road signs that tells you, yes, you're on track to make it to the next city. Yes, if Saint-Jérôme is five hundred kilometres ahead or something of that flavour.

BTB
Better take this exit?

DR. MATHIEU LUPIEN
Take this exit and so on and so forth. That's very useful. So all these signs are like epigenetic bookmarking of the human genome. It tells the system which route to take in order to reach the endpoint that's desired.

BTB
Give us a sense of how important is understanding that to helping us with understanding cancer and how it starts in the body.

DR. MATHIEU LUPIEN
All right. So again going in around 2005 and in subsequent years, individual labs like my own, as well as international efforts, were put forward to effectively annotate all the maps of the human genome — all the maps that are unique to a brain cell, all the maps that are unique to a muscle cell, and so on and so forth. And so we engage in that process, over the years, to the point where now we have very good maps of over 100 different tissue types. So that within a single individual we can have a sense of which parts of the human genomes are being used to make a muscle cell, which parts are being used to make a neuron. I keep going back to these examples. But those are always the ones that I come up with. But definitely, we have these maps now. Of course in cancer there's a problem right. There's multiple different problems that can arise and having these maps is extraordinarily useful in being able to make sense of these problems.

Alright, so let's go back to this analogy of the human genome being the map of all roads and cities in a given area. And the fact as well that, for instance, in cancer that it's a genetic disease.

There is going to be mutations acquired that are going to promote — give rise to — a tumor. So if we think of mutations as meteorites that come crashing down on Earth: While some will fall on a road—that's gonna be a problem.

So that's a cancer, that's a mutation that we would call a driver mutation because it's a mutation that destroys the road that you're supposed to take or destroys the city that you're supposed to end up in. And that's a major problem. OK, so those are driver mutations—they change the landscape. Now, you can also have what we call passenger mutations. So that would be, for instance, a meteorite that falls far in the forest where nobody lives. You wouldn't see it right. It would not impact your road. You'd still be able to make your way all the way out to whichever endpoint you need to make. And so having knowledge of these maps allows us to discriminate these mutations that are doing something—contributing to cancer development—versus not having much of an impact.

BTB
So in terms of the meteorites that you're able to identify [as] landing on roads that block our travel—take us to that step of how that helps you perhaps predict, or at least understand better, the beginnings of cancer in the body.

DR. MATHIEU LUPIEN
Alright, so one of the major discoveries that we made in the last eight years was the following. Before the human genome sequence was completed, before we could effectively annotate all these maps, the focus had always been put on the genes. The mutations in the genes are the drivers. Those were the driver mutations. OK. And that's why then we had this term "oncogenes"— because we had genes that we could easily identify as being commonly mutated in specific spots. We also had another term at that time put forward, which was "tumor suppressor genes" which were genes that once destroyed would actually no longer be able to prevent cancer from arising. So you had the two positive and negative forces. But still those were identified based on having mutations falling within those genes. Now, having access to the entire human genome—acknowledging that there is more than just genes—what we actually realized was that most of the mutations actually that make a tumor a tumor, most of the mutations that assist in developing and progressing and allowing for the development of a cancer cell, don't map the genes. The vast majority map outside of genes. The vast majority actually specifically target those light switches and those dimmers, because it's a whole lot more effective to simply regulate—increase a little bit or decrease a little bit—the expression of a given gene to change the nature of a given cell.

BTB
Just so I understand—sorry to interrupt—but the cancer cells are originating then in that dark genome?

DR. MATHIEU LUPIEN
Yep. A lot of it does.

BTB
Not just in genes?

DR. MATHIEU LUPIEN
Not just in genes.

BTB
So that is… you're advancing the field here, in terms of an understanding of where cancer comes from?

DR. MATHIEU LUPIEN
Right. So if we go back again to this analogy of the light bulb—so if you want to change the mood in a room, what's the most effective?

BTB
Candles.

DR. MATHIEU LUPIEN
Yeah, exactly. Right. So it's not the break. It's not to break the light bulb because then you go from too much light to not enough light. The best way to change a mood in a given room is to simply dim down the light or dim it up, depending on what you want to do. Or start flickering. Like, if you want to have a discotheque, you just light flickering that light bulb, right? It's going to be much more effective. Same principle. If you want to change a normal cell's identity and bring it to more towards a cancer cell identity, play with the light. Increase it a little bit more, dim the lights, increase the lights start, flickering it. And that's what goes on.

BTB
So these elements in the dark genome are critical to really understanding the full picture of how cancer gets started in the body?

DR. MATHIEU LUPIEN
Absolutely. And so that's why in today's world we're moving more and more towards an approach where we don't just look at genes, but we take a comprehensive view of mutations across the entire genome to try to make sense of the nature of someone's tumor as opposed to someone else's tumor.

BTB
Is there a particular paper, then, that you're proud of that you might want to direct us to that we should know about? Or maybe you could tell us about it.

DR. MATHIEU LUPIEN
So this is a very interesting concept. Again, going back to the underlying principle of science. Each paper is like a chapter, if we're lucky, or a big paragraph to a full story that we're all trying to write. And the other concept is also that, it's not a book that we're going to write that's led

by a single author—there's hundreds and thousands of author around the world. So to point you to one paper as opposed to a collection, a body of work, would be very, very difficult. This is an international effort. There are scientists here and we can be proud that we're leaders in a number of fields, but that also work in partnership with scientists and the U.S. and China, you name it. All over all over the world. And so to point you to one paper, as opposed to another, would be a little bit more challenging than I would like.

BTB
Then if you don't mind match you paint a picture for us of—if we came to your lab, what's happening in your lab today?

DR. MATHIEU LUPIEN
Right so. So what I've discussed is what we've done so far. So now we're already embarking on the next phase. And so the next phase allows us to keep making more sense of how mutations found just about anywhere in the genome can contribute to cancer. But what we're realizing, as well, is that in cancer the roads change independently of meteorites. And so the signs are changed. So you might normally think that you can make your fastest way from one city to another by just following the signs that are out there. The problem is that a cancer cell will change those signs. And so it has nothing to do with genetics. It's not changing the road, per se, but it's going to put you on a different road. And so instead of making your way directly to wherever you want to go, you'll be taking a huge detour and that detour will slow down your cell's ability to be fully reaching its potential. And so in that process it might transform and become a cancer cell. So these things all work together. So that's where we are right now. We're looking at how the signs are being changed with or without mutations. So with or without the meteorites.

BTB
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 Cote, and we're speaking to Dr. Mathieu Lupien, senior scientist at UHN's Princess Margaret Cancer Centre.

Mathieu your study now of this dark genome and how it relates to the genesis of cancer—what's your sense of where is this field of study going?

DR. MATHIEU LUPIEN
So definitely technology development is a huge contributor to how far we can go. Our goal is always to go as far as possible. To be able to predict where we're going? It is very difficult because scientists are adapting. We're constantly re-analyzing the data that we have, constantly generating new data, and adjusting our hypothesis based on what the data is telling us. And so to be able to effectively predict where we're going is a challenge. But definitely right now there's a strong push towards ensuring that we are as comprehensive as possible in our analysis. So now we've made the transition that this notion of looking at one gene at a time or to only be looking at genes—we're done with that. Now we're truly taking a comprehensive

approach to the entire genome. We're taking into account all the DNA sequences—all these single letters that make up the human genome and how they are changed in one tumor, for instance, or not. So how mutations are changing the code. And now we're gradually adding all these additional layers that I mentioned about, like the bookmarking—those road signs that influenced the roads that are made available within the cell versus another cell.

So just to give a perspective, with regards to mutations—that's one layer of information. Now that we start looking at road signs, we're talking about hundreds and hundreds and hundreds of alternative layers of information that can dictate the path that are made available in one cell versus another cell. And so we're just embarking in that process. And so I expect that we'll be definitely doing major leap forwards by investigating exactly what these layers have to provide information-wise, with regards to normal state versus disease state.

BTB
Give me a sense that, if…you're a young guy—what's your dream, in your lifetime, of this leading to, in terms of impact?

DR. MATHIEU LUPIEN
So every day is a dream as far as I'm concerned because every day we discover something new and that concept is what drives us to move forward. It's the concept of being astonished by a new discovery that fuels our imagination. What's the end point? I don't know that there is an end point but it's a path that's extraordinarily enjoyable. And the key concept is really to make the most that we can make of it to better understand how life is structured and built so that we can better understand how it's disrupted and disease. But it's an everlasting journey.

BTB
It strikes me also that, like the discovery of, say, for example, these elements in the dark genome in these other you mentioned that the meteorites and the road signs—these are things that you've discovered in just, what, less than the last 15 years? Which is a long time to us in human years. But I am guessing it's a nanosecond when it comes to research.

DR. MATHIEU LUPIEN
The pace at which research has picked up over, I would say the last 30 years, has been impressive. And so we're constantly adjusting what we do and it's extraordinarily challenging but extraordinarily amusing as well at the same time. But, so, I can tell you from my own experience the research program that I lead is in constant evolution. Some of the research we did 10 years ago we still do some of it, but it's probably now accounting for a third of the ongoing research in my group. Now we spend a lot of time in looking at other aspects that we could only really start looking at in the last five years or so because of technology development. But now we can and so we do it.

And so research lab in today's world have to be able to rapidly adapt to the changing landscape—changing landscape both in discoveries as much as in technology.

BTB
And I guess, my sense is this underscores though that something we often forget, is that, you know, everyone wants a cure of course for things like diseases, like cancer. But research takes time, doesn't it?

DR. MATHIEU LUPIEN
The transfer of information, like, from the first discovery to it making its way in the clinical domain can take decades. Absolutely.

BTB
Is that frustrating for you?

DR. MATHIEU LUPIEN
That's part of the process. We try to accelerate this as much as possible but it's part of the process and it's because we do our due diligence. It's because we want to make sure that our discoveries are correct, that they're, they're reproducible, they're robust and such that we don't bring anything that's false all the way up to the clinic. So by the time it reaches the clinic, the scientific community is very much aware of the positive and negative aspects of what the technology or what the discovery has to offer. And so in that line of thought, I think it's an important process to be diligent as opposed to speeding things through.

BTB
I've heard one scientist actually say if you can't handle failure you shouldn't probably be in scientific research. What's your take on that?

DR. MATHIEU LUPIEN
Absolutely. You need to love to be criticized. That's a given. Yeah exactly it's part of the…So there's different ways of criticizing individuals or being criticized right? There can be constructive criticism. So that's one. So, and that's all fine. And that one is always appreciated. And then independently of this, it's true 90% plus of what we do will fail. And that's just because we…I don't know I put a number out. Definitely depends on the individuals. Some would say it's only 10%. But I'm okay saying that 80%, or plus, of what I've tried has failed because you need to be imaginative and you need to think outside the box and you're exploring something that no one has ever explored before. So the key question is are you correct or not? Are the tools that you have access to capable of addressing the question you're putting forward? And is the biology completely different from what you expected it to be?

And so the key thing from a scientific perspective is our ability to constantly analyze that data and reassess. Reassess and reassess and reassess. So when I put down a number like 80%, it's not 80% of research that we invest in for years and years and years. It's 80% or so—whatever the percentage is now for research—that we initiate and we have some results and we realize that these results don't fit with the initial hypothesis and we readjust our hypothesis. It has to be able to move forward. But in terms of moving forward it's not an 80% failure. In terms of moving forward it's a 90% plus success rate. We always move forward and we always make

discoveries and we always deliver. It's more an issue that we deliver because we readjust, we reassessed. Because when you explore the unknown—I mean, none of us has absolute knowledge and so we have to agree with this and just acknowledge that not everything that we come up with as a hypothesis will be correct and adjust along the way.

BTB
How much for you…how important for you is the notion of team or collaboration then in this process? Because it sounds mind-boggling what you're trying to stay on top of, make your adjustments, keep learning and advance?

DR. MATHIEU LUPIEN
And I would say that in today's research it's even more important than it used to be to be a team scientist, because there's just so many fields of expertise that I've reached a level where no one can be an expert at every single one of them. And if you want to be able to make the most impactful, the most game-changing discovery, you benefit from interacting with your peers. You benefit from reaching out to individuals that have expertise on different aspects of research, and so from my point of view team research is not only effective, but it's the most promising avenue for the future of research.

BTB
What's the road been like for you, so far? You're roughly what, 13, 15 years into your career. After graduating with your PhD, what's the road been like for you?

DR. MATHIEU LUPIEN
It's been fun and that's why I'm still here. Happiness is key and so every morning I come to work and I'm excited, again. So I grew up with as a kid with this notion that I translated one day to astonishment as the source of imagination. That's what drives me.

BTB
Who wrote that?

DR. MATHIEU LUPIEN
So, it's, I remember it as a kid being something that was portrayed in one of those shows. So, *Sol et Gobelet*, to be very specific, was a TV show that I watched as a kid which was meant on educating kids. And I remember, I don't know why, but that single sentence stuck with me for the rest of my life. Astonishment is the source of imagination.

BTB
You could write that on your lab wall.

DR. MATHIEU LUPIEN
I say it often enough that I don't need to write it but yes.

BTB

You're what's known as a pure scientist, am I correct? Your time is spent 100% in the lab writing papers. You don't see patients. So what keeps patients top-of-mind for you?

DR. MATHIEU LUPIEN
Well that's easy right? I work on cancer. I worked on predominately breast, prostate cancer. I also do some work on brain and leukemia. It's easy. Cancer is personal, right? For every single one of us in the research labs. We all have someone close to our heart that's either currently going through treatment or that recently passed away from cancer. And so the motivation is very, very, very easy. It's really personal.

BTB
I understand you also carry a small reminder of your mission. Every day. About what, to remind you of what this work is all about. Wherever you go. Can you tell us that story?

DR. MATHIEU LUPIEN
Yeah so. So we all know Terry Fox. We all know that Terry Fox has been the image of cancer research in the country. And so when I was a kid Terry Fox, was, I was too young to remember him *per se*. But growing up as a scientist, every single lab that I had the chance to work in always had a picture of Terry Fox somewhere. We always had a reminder of Terry Fox. When I went to the U.S., Terry Fox was not so commonly seen in the US. But at one point they came out with these loonies that had Terry on it. And so the first one that I grabbed, I kept it. And I always have it with me. It's in my pocket. I always have my Terry Fox loonie with me as a reminder of what we do and why we do it. I think he's a great example of commitment and a reminder of the importance of the work we do.

BTB
You're carrying that right now?

DR. MATHIEU LUPIEN
Yes.

BTB
Special to you?

DR. MATHIEU LUPIEN
It is. And it's been there in the pocket every day.

BTB
What's your approach to mentorship? Inspiring the people in your lab that you work with every day.

DR. MATHIEU LUPIEN
So my mode of operation is to provide them freedom. Freedom to think, freedom to act, freedom to be, to achieve their full potential. There's nothing more important in my mind than

freedom. And it's interesting, because at the same time it's scary. Because when you have freedom, you have to you have to take into account the responsibilities that come with it. And, typically the trainees adjust very quickly and they learn to appreciate this notion that, yes, they can think independently and engage with me as if I was a peer, as opposed to their professor, mentor or boss. And that makes a huge difference because we can engage in arguments about how the system works, how we should formulate our hypothesis and they feel totally confident in moving forward with their hypothesis and discussing it. They don't shy away from voicing their opinion and I think that there is nothing more important than that for a young scientist to develop and to be able to become a leader in the field of cancer research.

BTB
So you foster an environment where you're challenged by them?

DR. MATHIEU LUPIEN
Absolutely.

BTB
And you're okay with that?

DR. MATHIEU LUPIEN
Absolutely. I love it.

BTB
That's great. Is there a mentor in your life or career who stands out?

DR. MATHIEU LUPIEN
Absolutely.

BTB
What made their presence so critical?

DR. MATHIEU LUPIEN
So, Miles Brown, who was my mentor during my post-doctoral training at the Dana Farber Cancer Institute in Boston. He's the one that first gave me freedom to do everything that I wanted the way I wanted, and that just pushed me beyond the boundaries of my initial limits, so that I could actually achieve more than I would have without that freedom. And yeah, absolutely. He's embodies the ideal scientist and my perspective—being excited about discoveries whether it's his own or that of others, acknowledging the quality of the work from others, and always, always, always encouraging his people to be as independent and free in their thoughts as they can be.

BTB
Now there is another mentor from your past that I understand inspired you as well. A famous hockey player. Can you tell us about that and why?

DR. MATHIEU LUPIEN
Why are you referring to a Maple Leaf player?

BTB
Are you kidding? A good boy from Quebec, are you serious?

DR. MATHIEU LUPIEN
Yeah I know correct. Yes. Well, growing up, yeah—so determination, right? Examples of determination. You mentioned in the introduction that I had as heroes Marie Curie, Louie Pasteur and the like. I also had access to books back then that showed the contribution of Maurice Richard to all that he's done—so many Stanley Cups and the like. So, I always had him as a hero of determination. Clearly, he succeeded in that field.

BTB
What advice would you give young kids out there? Like today's kid from Saint-Jérôme who's interested in the study of biology or life or science?

DR. MATHIEU LUPIEN
So my first advice would be reach out. Because you can't know what you might be getting yourself into without engaging with those that are doing it. And so any kid for instance that…

BTB
But I can't walk off the street and call up Mathieu Lupien, and go "Hey, Mathieu, I'm a 16-year-old kid interested in biology. What do I do?"

MATHIEU LUPIEN
Why not? Why not?

BTB
I guess we'll put your email at the end of the show.

DR. MATHIEU LUPIEN
Please do. I have no problem with that. I mean, if there is one reason that I managed to make my way through all the different phases of my education—go to McGill, go to Harvard and come here afterwards—it's because I never shied away from engaging with individuals that I thought that I had to engage with. Yes. And we're approachable individuals. We're approachable. I mean, it's just that, you have to reach out to us. And sometimes you have to be imaginative because you can imagine that we don't have only one request today. We have…our workload is definitely keeping us very, very busy. So if you're approaching us in the right way that we notice, we'll engage for sure.

We want to train the next generation. I mean it's—I've often gone to schools to teach them and explain to them my career path, and typically the kids are so excited to hear about my career

path or anybody else's, right? They want to know what's out there, and so any kid that's out there should not shy away from reaching out. If you like something, go talk to the person that, according to you, is the person that's providing for the most exciting research or work in the line of thought that you have.

BTB
That's great advice. What's next for Mathieu Lupien? What should we be watching for?

DR. MATHIEU LUPIEN
So again, we're definitely engaged in doing more exciting research that can transform care and I would say the fact that we're here at the Princess Margaret Cancer Centre is a huge asset because as you've heard from the start I've been heavily engaged in research that's at the forefront of discovery. Potentially some would argue at the forefront of fundamental research. Being here at the Princess Margaret implies that we have the chance to regularly interact with the doctors—with the clinicians—that see patients, that can inform us of what's really needed in the clinic today and of their exact needs. And vice-versa, we can teach them about what's to come. And so this two-way conversation is fabulous, because it ensures that we work on what's most relevant. And at the same time it maximizes the likelihood that any of our discoveries will be up taken by the clinic to make an impact in care.

BTB
Dr. Mathieu Lupien, senior scientist at the Princess Margaret Cancer Centre. Thanks for speaking with us. And continued success in your research.

DR. MATHIEU LUPIEN
Thank you very much. It was a pleasure.

BTB
For more on the podcast go to our website, www.behindthebreakthrough.ca. And if you have any comments about the show please let us know. Rate the podcast wherever you're listening — we crave feedback.

That concludes this episode of 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 Cote.