Season 2 – Episode 10 – Dr. John Dick

Transcript

CHRISTIAN COTÉ:
Hello and 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 Coté and joiningus today, Dr. John Dick, award winning senior scientist at UHN's Princess Margaret Cancer Centre and the Mcewen stem cell institute. Dr. Dick's research has transformed scientific thinking around the world about how cancer starts and grows, helping to spark the move toward more targeted treatments to eradicate the disease. Dr John dick, welcome to Behind the Breakthrough.

DR. JOHN DICK:

Christian, it's wonderful to be here. Thank you.

CHRISTIAN COTÉ:
If we could start off big picture, because I know your Research has largely focused on how cancer and specifically leukemia get started in the blood, which is, I understand, also intimately intertwined with stem cells. So, before we get into the detail of your discoveries, could i ask you to. Maybe first give us a primer on blood and stem cells using your pyramid imagery, maybe?

DR. JOHN DICK:
Sure. So, the way I'd like to describe you know, what the blood system is, is if you think about a pyramid you know on the ground, you have the peak at the top, the wide base at the bottom. And think aboutthe blood system. So, the blood is composed of about you know a dozen cell types. So, you can have you know, red cells, you have immune cells of different types monocytes which involve clotting and plaiting and things like that. So these are cells that are made about a dozen of them. And many of these cells are very short half life. So that's the base of the pyramid, you know, billions and billions of these cells in your bloodstream. And in fact, they think that the blood makes almost 10 to the twelfth. And that's a massive number of cells every single day.

CHRISTIAN COTÉ:
Wow!

DR. JOHN DICK:
Now many of these cells have a really short half-life? And what that means is that, let's say, you know, less than a day. And so, they need to be constantly replaced and they're replaced with cells that area little further up the pyramid that we call progenitors. And the progenitors are primed you know, they have a progenitor for red cells there's a progenitor for the platelets, there's a progenitor for you

Know, immune cells and so forth. And so, these progenitor sense that there is a need and they get activated and they proliferate like mad and differentiate, that means that they end up making you know, a mature redblood cell, for example.

And so those cells do that job on a you know, on an ongoing basis. But of course, when those cells are gone, they need to be replaced by cells that are further up the pyramid. And ultimately, the whole system is driven from stem cells that are at the very apex of that pyramid. Now, again, as we go up the pyramid, the frequency of these cells you know, reduce it. So that, for example, the frequency of the progenitor is you know, maybe one in a hundred. So, one percent of all blood cells or those progenitors further up the pyramid, it's point one percent. And youget to the stem cell, it's like the needle in the haystack. The stem cell is something you know, like perhaps one in a hundred thousand cells or so is a blood stem cell in the system. And so this is the blood system is driven from stem cells to the very top.

CHRISTIAN COTÉ:
Can I just ask you, john, that needle in the haystackoriginating stem cell, what's the shelf life of that stem cell?

DR. JOHN DICK:

Probably a lifetime. You know, it's been studied best in the mouse. And you can take a single blood stem cell transplant it into a mouse. And I'll explain a transplantation in a second transplant in a mouse, and it will regenerate the blood of that mouse for its lifetime. You could take cells from that mouse transplant into another mouse and that stem cell will have self renewed and it will also regenerate blood for another mouse. And it can do that a couple of cycles. And so, asingle blood stem cell has an enormous capacity beyond a single life, so to speak. At least that's the context in the mouse. I mean, the human, we don't know, but you know, we think that they last a lifetime.

CHRISTIAN COTÉ:
So, your research, in essence, focuses on how healthystem cells are responsible for generating new blood cells and can transform into cancerous stem cells. So, I'm curious, when you first arrived on the scene as a young researcher in Toronto back in the mid 80s, what were you seeing as the gaps in knowledge of stem cell and leukemia? What did you know and not know?

DR. JOHN DICK:
so, everything we knew about blood stem cells, the normalblood stem cells, you know, was based on the pioneering experiments of till and Mcculloch, these tremendous pioneers of this field who carried out the seminal work in the early 1960s where they basically you know, ushered in the era of modern stem cell research. So, how do you study stem cells right? They're really rare. And you know, it was true in 1960 and it's true actually today. It's really hard to grow a blood stem cell ina lab dish. And the towering achievement of what, till and Mcculloch did in 1961 was that they figured out that you could actually study blood stem cells by transplanting them from one mouse into another mouse.

Now, what you do is you irradiate a mouse. If you give a certain dose of radiation, the blood is the most replicative tissue in the body, and that makes them very sensitive to radiation. So, if you give a dose of radiation in eight days, that mouse is going to die because it doesn't have any blood.Now you can take cells from another mouse of the same species, and it's not going to reject it because you're not crossing any immune barrier, take cells from one mouse bone marrow cells from one mouse, transplant them into that mouse that's going to die in eight days, the day after radiation, transplant them into the bloodstream. And the stem cells, it turns out, from the donor mouse will regrow the blood system in a mouse.

And so, this idea that you can study blood stem cells by watching what they do and what they do is to regrow the blood system. And that's what they use to figure out what was a blood stem cell. And that set off the cascade of you know, research for the from 1961 until today, really, i would say the modern era of stem cell research. So, everything we knew when i started my work in the mid 1980s was based on what the mouse stemcells do.

And so, we inferred that that's what most stem cells do in all other organisms, including humans. Now, what was known by the time i started was that you can take a human, give them high doses of radiation or highdoses of chemotherapy, and you could to kill off their cancer cells. That's a big armament of cancer therapy. And you could take donor stemcells and transplant them in from somebody who was related. And they won't cause a rejection. Those cells will regrow. And so, we knew that you know, there were cells there. They must be stem cells because theyregrow in the blood system. But we couldn't put our finger on we don't know what they looked like.

And so, at the time, i started the only assays that were available, that ismethods to test cells that have some kind of proliferative ability was called a colony assay or a colony forming assay. So, this is where you take bone marrow cells. You put them into gelatin essentially with a whole bunch of goodies. And what will happen is that there are cells that we call progenitors, which will grow colonies in that gelatin. You could look under a microscope and say, oh, that's a colony composed ofjust red cells, or there's a colony composed of just you know certain kinds of white cells. And over time, you know, many investigators had worked out what we thought these progenitors were.

But the problem was that you couldn't be sure that these were blood stem cells. They were could be just these progenitor cells. Remember mypyramid, they could be partway up the pyramid, but not necessarily at the peak. And so, based on the idea that in the mouse system, the only cellthat is a true stem cell is one that can regrow the blood system. If you transplant it led to the idea that you know maybe that's something we could test in the human system. But of course, you can't do experiments on people, right. Nobody wants to volunteer for my experiments. And so,

What happened was that i had a colleague in Toronto, Bob Phillips, whodid, pioneering work on a mouse called a skid mouse. This is an immune deficient mouse.

So, I don't know, people might remember, remember the bubble boy? And heused to remember, this is a boy who was born with an immune deficiency. And basically, you know, you're very susceptible to infections and this child is going to die very young. And so, they had this whole module set up for the moonshot because they weren't sure what kind of bugs astronauts would come back to. And they set up this whole big rooms of clean rooms so you wouldn't spread any bugs around. And so, they weren't using them because they didn't realize astronauts didn't need this, when they came back and they put the bubble boy in that room because they kept him in a sterile environment.

So, bob had a mouse equivalent of that disease. So, these mice didn't have t cells and b cells, which are the main armaments of your immune system.

CHRISTIAN COTÉ:
Right.

DR. JOHN DICK:
You know, it's one of those quirks. I was talking to a postdoc one night. We were just brainstorming about a couple of different ideas. And they'll relate to something we're going to talkabout in a second, which is leukemia.

And we just had this idea and I don't whether it's his idea or my idea, I thinkit was just collectively us, because he had gone to a talk that day and somebody had talked about transplanting rat cells into immune deficientmice. So, you could have a rat into a mouse. So, the idea was, well, what if we could take human cells and put them in a mouse? And I knew that that wouldn't work because, of course, you know, a mouse has an immune system and it's going to reject the human cells. But I knew that bob had this really, really good immune deficient mouse. And i went to him and I said, bob, what do you think about if we put human cells into a mouse? Andhe said, you know, john, it's not going to work. In 1961, or ‘62 or ‘63. Many people after till and Mcculloch's pioneering experiments tried to put human cells into an irradiated mouse and nothing you know, nothing happened. But, of course, you know, I said, but, bob, there's an immune barrier there.

And so, that led to these experiments that we ended up doing where we ended up getting his mice, putting human cells. And it turns out there's enough complementarity between what a human cell needs and what a mouse can provide. And so, now we had mice running around that had a little bit of the mouse’s blood actually being human. They were human cells that were growing in in the mouse examples. And so, this set off thebeginning of this idea that you can actually study human stem cells by watching what they do, and you're not encumbered by the you know, complications of doing clinical research and actual people.

CHRISTIAN COTÉ:

so, let's turn to one of your first major discoveries, which is going back, i understand, to early 90s, like around '94 when youidentified the stem cell that causes leukemia. Can you talk to us about that finding?

DR. JOHN DICK:

sure. So, when i set my lab up, you need to understand thecontext of what was happening in the field at the time?

CHRISTIAN COTÉ:

absolutely.

DR. JOHN DICK:

so, there are two big rushes. The big rush in cancer research in general was the discovery of oncogene right, the idea of, cancer causing genes, that we have embedded in the DNA of a cancer cell,one of our normal genes that's gone bad.

DR. JOHN DICK:

right.

DR. JOHN DICK:

and these are genes that control growth. They can either cause cells to grow too much or they don't die enough and so forth. Andso, this was the big discovery and sort of the early, late 1970s, early 1980s, many people were discovering these oncogenes. And so, the big push in cancer research was let's find cancer causing genes. So, these are genes that became they're normal genes that became mutated and that set off the cascade of cancer growth. And so, people were studyingyou know, these oncogene mutations. They were starting to be discovered for leukemias. Now, i had done my post-doctoral research in the lab of dr. Alan bernstein at the Ontario Cancer Institute, Princess Margaret Hospital, on gene transfer. So gene transfer was just discovered in that time.

In fact, i would say some of our work led to that whole feel. Right. The idea that there are people who have genes that are defective for you can think about immune deficiency, the boy who had a deficiency of their immune cells, there's a gene that's missing. There's a disease called thalassaemia or sickle cell anemia. These are diseases of red cells, a single gene that you can think about replacing that gene in the blood cells of that person. And so, there was a big impetus to take viral vectors, to harness viruses. They're just cousins, if you like, of the hiv virus. You can engineer in any gene. You put a human gene into them. These are very infectious, and you can infect them into the blood cells of a person.

And so, the beauty of this was that you could take blood stem cells froma person who needs some deficiency. You could then put the gene that they're missing back into their cells and then give them their own cells back. So, the beauty is that you harness the power of blood stem cells toregrow the blood system. And you don't have to worry about immune rejection because they're your own cells in your own perfect match to yourself. So this was all being developed at that time. I was just setting

Up my lab at the time, and my colleague down the way was somebody whostudied oncogenes, Tony Pawson a pioneer of this area.

And so, we thought, you know, let's take our gene transfer technology, put in cancer genes and let's put them into normal blood stem cells and make leukemia. Let's make cancer. Let's study the cancer process, but notin a mouse, but do it in the actual human cells. So that was one of the goals of the experiments that i wanted to start my lab on was to take our technology of doing gene transfer but putting in cancer genes intonormal cells and then watching the leukemia establish. So that was the one side.

But the other side of that experiment was that we wanted to study normal blood stem cells and we had just developed this technology of putting human cells in a mouse. And so, we had this whole program on studying normal blood stem cells. And what we showed was, of course, that the cell that regrows the blood system in a mouse looks like it might be a different kind of cell than any other cell that you know, these progenitor cells that are there. So, what happened was then, as we were thinking about putting, you know, cancer genes into our normalcells, nothing happened. And so, at one point we're thinking, well, what's the problem? Is the problem that we're not getting the gene into these cells properly? You know, all we were doing was we were taking normalblood cells, putting in the cancer genes and then watch them grow in a lab dish.

But we had already known that it's really hard to grow leukemia cells ina lab dish. So, this is one of those big paradoxes, right? You can have a leukemia which is growing rapidly in the bloodstream of a person. It's going to kill the people. You take those same blood cells, put them in a lab dish. It's really, really hard to grow them. And so, because we had this one side where we were already realising that we could grow normal, normal blood cells in a mouse, we said, how about if we just takeleukemia cells and put them in a mouse? Will they grow? If that would work, then what we would do is we would take our normal cells, put on our cancer genes and then put them into our mice, not put them in a lab dish.

CHRISTIAN COTÉ:
right.

DR. JOHN DICK:
and so that was the impetus. So, we weren't thinking about stem cells, leukemia, stem cells. We were thinking about anything like that. It was just very sort of methodical. If we have this, let's do this. Andso, we did these early experiments where we took human leukemia cells and lo and behold, they grow beautifully when we transplant them into our immune deficient mice.

CHRISTIAN COTÉ:
Interesting way to put it.

DR. JOHN DICK:

but, but then the question became, okay, does that mean that every single one of those cells would be able to be ingraftable, that it would be able to generate leukemia if we transplant it into a mouse? And so, we did these experiments where we took a bunch of mice, let's say 10 mice. We transplanted them with five million cells. We have another set of mice transplanted with one million cells and then another set transplanted them with one hundred thousand cells. And wewaited, which ones got leukemia? And it turns out that all the mice that got, you know, five million cells, 10 million cells, they always got leukaemia at one million cells, only about, let's say, you know, 20 percent,30 percent of the mice actually got leukemia and 100,000 cells, none of the mice got leukemia.

So, right off the bat, what that told us was, hey, maybe not every leukemia cell is equal in its ability to regenerate disease if you transplant it. And that made us think about our blood stem cells becausethat's what happens with blood stem cells. We knew that our blood stem cell was about a one in a million cell. In this assay, if we did the same thing with normal cells, again, only about one in a million cells would be able to regrow normal blood. And we know from all the work of till and Mcculloch that you had this pyramid, right? That one in million made one and a half thousand one hundred. And they made all the blood cells. And we thought, well, maybe what that means is maybe leukemia is set up like ahierarchy, like our pyramid, where there are only some cells that had leukemia stem cells.

Now, this is a little dark secret, i would say, of our research, and that it was that i only learned this, you know, maybe a decade or so after that. And that was that there were experiments that were done in the 1960s, a whole series of papers that i actually never read where people were predicting that there was such a thing as a leukemia stem cell. Now, whati did know was that till and Mcculloch had developed one of these colony assays for leukemia. Right. So, they were also thinking about the idea of taking leukemia cells. In this case, aml. Putting in a lab dish in these colony assays these gelatin assays. And again, they ask, does everyleukemia cell make a colony or not? And it turned out that only one in a hundred made a colony.

We call that a clone agentic progenitor in leukemia. And so, they talked about that as being potentially a leukemia stem cell. So, when we got ourdata to say one in a million or so was a cell that could engraft a mouse. So, you could you could think of it in two ways. One is it's a really lousy or crappy assay to find this one in a hundred cell is colonogenic progenitor that Mcculloch and till and others had been working on. It's just a very inefficient way to find that cell. Or is it like the blood systemwhere you have a stem cell which is more rare, different, more primitive than these colony forming cells? And so, the only way to prove that wasif we could isolate that cell in this case of leukemic initiating cell, that one in a million cell, could we fish it out of the million cells and say,

Here's a cell? It always does this job. The other nine hundred, ninety ninethousand cells will never make leukemia.

So, that would say it's not just the inefficient assay if it's inefficient assay, it doesn't matter if we sorted cells. Every population would always give us some ability to make leukemia in a mouse. But if it's only a special cell, that does it and we could take leukemia cells, dispense theminto pots using special sorting technology, take the ninety nine percent of the cells, put them in one pot, take the one percent of the cells, put them in the other pot, put them into our mice and we only get leukemia from one of them. That would prove it was the leukemia stem cell and that's what happened.

So, in 1994 we did that experiment. Tsvee lapidot was a post doc in my lab. We didn't have that sorting technology in Toronto at the time and i had made connections with a group in Rochester and buffalo at Roswell park. And so, we got our cells in you know dry ice, went across the border. Customs control was a little unusual thinking, but why are these scientists from Canada coming across the border? And on top of that, tsvee lapidot is Israeli. And so, he had a passport that you know was hebrew and the guy was looking at his passport and it was a little bit to get us across the border. But we did. We sorted our cells all day, got back in the car, drove across the border, came back to Toronto, injectedthem in our mice, and then we waited. And in that case, a couple of weeks later, we opened our mice up. And sure enough, one population of mice had leukemia and the other ones never had leukemia. And so that was justthe aha moment. Right, that we realized that, wow, you know, we've uncovered something. We've uncovered a stem cell for leukemia.

CHRISTIAN COTÉ:
You still get excited by that.

DR. JOHN DICK:
you know, it was thirty, thirty years ago. And I still youknow,

CHRISTIAN COTÉ:

You're jumping out of your chair practically. People can't see, but you're jumping out of your chair. Ok, could you step back then? John give us then like the significance. Tell us what this means, thisdiscovery how it say shaped future research from that point on?

DR. JOHN DICK:
Sure. I have to give you sort of two answers to that question to different communities. So, I would say that for the blood community, for the leukemia community, I think people looked at that dataand said, man, that is that is really nice. That is really great. And what these guys have done is they've proven a theory, a hypothesis that we've had for for 30 years. So they're, as I said, seminal work in the 1960's onwards where people had predicted that aml, this particular kind of leukemia, you know, had this hierarchy, you had lots of leukemia blasts at the bottom of the pyramid, and then you had these cloner genetic progenitors.

And what we did was we put another cell on top of that, right. It's like pinthe tail on the donkey. We pinned another cell on top of that pyramid andthat's an advance for that field. But, you know, was it a groundbreaking, novel thing for that community? No, because it was just it was in line withstem cell research based on what we know about normal cells, it's not such a big leap to think that leukemia is just a caricature of normal development and so forth. So that's the answer, i would say, for that community.

For the broader cancer community, which has turned out this work has had some underpinning change to it took a longer time for it to be accepted. It also took a longer time for just to be recognized. And that was that. It goes back to what i said earlier, and that is that by the 1980s, the main part of the cancer community was focused on cancer is a genetic disease. We need to understand the genes that go bad. And all of cancer research was focused on genes that have gone bad. You know oncogene research, finding cancer genes, figuring out how they worked.And in some ways, that field was begun by Eifel, called buckett biochemistry.

But the idea is you have a tumor. It's a bag of abnormal cells. You got thetumor, you mash it up and you do genomics, you do proteomics, you do biochemistry and you study how cancer genes, what are the cancer genes that are gone bad and how do they work? What we're saying was you can't just look at cancer as a bag of bad cells. You have to think about what each of those cells is doing, because in there could be only some cells that have these stem like properties. And that led to the other bit of thinking right, which is, ok, if you have bad cancer cells, are all cells equal? What we're saying is that not every cell is equally able to keep that cancer going. Right. Only some cells are able to keep them going. And the ability to keep it going is just like what makes a normal blood cell, keep the blood system going. It has this inherent property ofstemness or self-renewal.

And what our data was arguing was that only some cells in the cancer have that ability. And so, it means that the focus of cancer research should not be just on the ball of bad cells, but what the individual cellsare doing and what their properties are. You know, it took more than a decade for our leukemia research to be, start to be translated where people were picking apart their tumours into individual entities and testing what individual cells would do. And the two key pieces of work came from Michael Clarke and his colleagues at University of Michigan, who published the first paper in 2003 on breast cancer cells. Mike is a matter pathologist. He knew about our work and so they were thinking about these processes.

And so, they started to take the approaches that we developed in leukemia and applied them to breast tumors and put them into differentcells, put them into mice and ask what kinds of cells have the ability to remake breast tumors. And the other work published right around the

Same time, was done by my colleague peter dirks at the hospital for sickchildren, who studies brain cancer because my colleague, he was very taken by our work and he really tried to apply the same paradigm as to what we used in our blood leukemia research and apply them to brain tumors. And so, these two papers came out at that time basically saying we have to start thinking about what individual cells are doing in the tumor. So that began sort of the cascade of impact, i would say, into thebroader cancer community. It's taken time for that community to really adopt and accept, i think, some of these ideas. But it's definitely coming there now.

CHRISTIAN COTÉ:
right. And to that end, you talk about other studies and other people interested in what you discovered in the mid 90s. There wasalso, a trickle down effect eventually towards treatment. Correct?

DR. JOHN DICK:

as we came to learn more of what these cells do, what theylook like, why are they different? Why do they have this property of propagation, initiation of a graft in a mouse, what makes them unique and different? And in leukemia, you know, we really got one of major surprises. I mean, the other thing we think about is what's cancer?
Cancer is cells that grow too much. They grow in an uncontrolled way,but that is all around growing too much. And for seven decades, until relatively recently, our focus on cancer therapy has been to target cells that grow too much.

And that's where the chemotherapy is, to try to find that thin window, totry to target the cells that grow too much in the tumor without have the collateral damage of hitting the other proliferative tissues like your blood system, your gut, other cells that proliferate a lot in a normal context. And that's why you get a lot more toxicity. One of the things we realised when we studied our leukemia stem cells was that our stem cells were actually dormant or quiescent. They could lie silent for long periods of time, whereas the clonogenic progenitors, the ones that Mcculloch and others worked out in the blood system, they're highly proliferative every day they're replicating.

And that reminds us again about the normal blood system. Those progenitors that we have in the pyramid that are part way up from the base are proliferating like mad, but normal blood stem cells can lie dormant. In fact, the data now shows can lie dormant for years. And so, itlooks like leukemia cells have kind of adopted a bit of a chimera. They areable to proliferate more when they get activated. But at any one time, they look like they can be quiescent or dormant. And so, if you think about it, you know, the chemotherapy that was used when we started ourwork is all based on killing cells that grow too much. And that's true in aml, which is a disease that i study. And so, it means that these cells that are dormant, these one in a million cells, can be swimming in a sea of anti proliferative chemotherapy agents and they're not going to be touched.

And so, that right off the bat said, well, this could be a main mechanism asto why these cells are surviving. And so, from a therapeutic standpoint, what that means is we need to find whole different categories of drugs to try to target these cells, either to activate them into cycle and they become more sensitive or to target them in a different way. And at the end of the day, that principle is largely true for lots of cancer stem cells. That is the stem cells, not just leukemia stem cells, but the ones that are important in brain cancer. You know, breast cancer or other kinds of cancer is that often these cells have kind of dormancy type properties and that underlies some of their chemo resistance, how they can survive therapy.

CHRISTIAN COTÉ:
let's move it to '97. Another discovery for you. What I've heard termed as the elusive parent of all blood cells. What did that mean?

DR. JOHN DICK:
so, i mean, this is just sort of the practicality of research. So are '94 paper, which is the work that discovered leukemia stem cells was done on three patients. So, we had three animal samples we sorted, and we found the leukemia stem cells. But it turned out that each one of those was what we call a very primitive sample. So, so aml leukemia comesin different flavors. And for decades, you know, the clinical community, the research community tends to classify leukemia based on what the cells look like. In other words, if my leukemia cells look really primitive,they get binned into one kind of category. If they look like they're more mature, they've adopted kind of features of normal blood development. They're putting the features together abnormally because it's a cancer cell, but they're trying to put together features of normal development.

And so, you can classify patients into these categories. And it turns out that they will have different clinical features like different survival properties. Primitive ones tend to be more people fail therapy much morethan the more or differentiated kinds of leukemia. And so, we happened to study that one. So, the question then was, well, are these leukemia stem cells only relevant in a primitive kind of leukemia? And so, in '97, what we did is we took a few different kinds of aml. And what we were asking for is, does the leukemia stem cell look different in a leukemia, which is more mature compared to a leukemia, which is more primitive.

CHRISTIAN COTÉ:
sorry, and primitive john, means less developed?

DR. JOHN DICK:
Yes, more stem like actually. So, remember a single fertilized egg that we all start from? It's a single fertilized egg. It doesn't look like a leukemia cell, liver cell, the brain cell or anything that has time. It differentiates, it matures different case organs. But theblood system is like that. The stem cell at the top is a primitive cell. It doesn't have red cell features. It doesn't have immune cell features. But as it develops, it starts to choose which program it wants to become. And then it becomes a red cell, a t cell or so forth. And so, there are

Features that these cells have either gene expression programs or theyhave proteins on their surface that you can test very easily with certainkinds of technology. So, a cell that's going to make a red cell has a different kind of set of proteins on its surface than a cell that's going to become a t cell.

And so, we can just take those equivalents of normal and layer them onto our leukemia cells and ask, what does this leukemia cell look like?
Does it look like it's a cell that's more stem like, or does it look like a cell that's trying to become some kind of a white cell? What happened was, again, there was research that had been done a few decades before ours. And this is in fact, it's true today. It's true across cancer types. Andthat is often you look at a cancer and you look at what it looks like. Does it look like a more mature cell or does it look like a more primitive cell? And there is an implicit concept that what the tumor looks like reflects the cell that it came from. In other words, if a cell that's already making its way to becoming a mature white cell gets transformed, it gets an oncogene in it that stops development at that point, causes the cell to grow too much. And that's why those kinds of leukemias look like that.

Or if it happened in a stem cell, the cell hasn't started to develop or differentiate. And that's what those leukemias look like. So, the featuresof the leukemia reflect the cell of origin. But the alternative hypothesisis all tumors start in stem cells. But the nature of the oncogene the cancer causing abnormalities are impairing the ability of that cell to develop far enough down, if you like, the pyramids. So, for example, everybody starts in the stem cell. But some oncogenes only let that stem cell go down a very short ways down the pyramid and then the leukemia happens, or other kinds of mutations allow it to go further down. And then, the leukemia establish but they all start in the stem cell.

And so, this was a question, in fact, till and Mcculloch raise this in a review at least a decade before we started our research. And so as we were doing our research, we thought, you know what, maybe we can testthis idea. And so, we took leukemia's that we're more mature, leukemia's which we're more primitive. And we asked what do their leukemia stem cells look like? And it turned out that leukemia stem cells looked very similar, very identical. So, it didn't matter what the features or the phenotype of the classification of the leukemia, they all had leukemia stem cells that kind of looked all the same. And interestingly, the features, the cell surface proteins that we use to sort of leukemia stemcells were actually very similar to the proteins that we used to sort of normal stem cells.

So, normal stem cells had a set of properties and we could see that in our leukemia stem cells and it was in the leukemia stem cells for matureor primitive. And so, what we argued in that paper was that this perhaps speaks to the idea that the cell that starts leukemia is actually a bloodstem cell because the leukemia stem cells look like a normal stem cell.

That set up quite a bit of controversy, I would say, and in fact, still beingtested today. But that actually set up, you know, a series of studies thatin one way or other we've been involved with for a long time and made some progress in recent years in somewhat of a different way, where we've been able to, I think, to gain some insight into you know, where leukemia starts.

CHRISTIAN COTÉ:
so, what are you seeing in terms of impact from the '97discovery? What's decades later? What's been the cascading effect?

DR. JOHN DICK:

I would say the cascading effect for that one is more on the research side. It's more on the the focus of research. Right. So, so what happened you know, actually, kind of after that was many people tried to test these ideas using mouse. It's much easier to do in a mouse. You could sort mouse stem cells, mouse progenitor cells put in oncogenes and in an experimental way ask which cells are sufficient to cause leukemia. And depending on the oncogene, depending on the cell that's used, you know, people are getting answers that span the gamut. Right. So sometimes both stem cells and progenitors could initiate leukemia if you engineered an oncogene into them. Sometimes it was onlythe stem cell.

But the question then became, well, ok, that's a mouse. But you know, a mouse is different than a human. And a mouse is actually much easier to cause cancer in. And that's true for almost any tissue in a mouse and justgrow it long enough in a lab dish. It'll actually turn into a cancer. In the case take blood cells and turn into leukemia, that never happens in humans. So, the constraints that we have on our cancer prevention process are much stronger in humans. You know, mouse lives two years we live you know 80 years, we make you know, a lot more cells, right? I mean, there's this old notion that a mouse makes as much blood in its lifetime as a human does in one day.

CHRISTIAN COTÉ:
wow.

DR. JOHN DICK:
So, if you think about the stress demands on your stem cell,they're quite different, right, between those two organisms. And so, our whole focus you know, over the course of my whole career has been we only work on primary human cells.

CHRISTIAN COTÉ:
I want to read you something, john that you said after the 97 paper. You said by pinpointing stem cells, we can test how they cango wrong and find a way to target them. So, I'm curious what progress has been made on that front in terms of targeting since then?

DR. JOHN DICK:
the answer to that question, you know, has ended up being areally fundamental question, not just in cancer research, but in all of stem cell research.

And that is what makes a stem cell a stem cell. It's not just making the blood system you

know, or making a lot of something, which is what you think of stem cells, that stem cells makes a lot of something. It makes a lot of a tissue. But in fact, a lot of the properties of a stem cell are dormancy. It's just when it gets activated, it gets activated and it does a whole lot of things. But what is the essence of how it can do that without exhausting itself? Right. So how does a stem cell regrow the blood system but do it over a lifetime so you don't exhaust the stem cellthat you started with? How does it maintain itself?

And that's this property, almost mysterious property called self renewal. And honestly, today, we still don't have a really full grasp on what are the features and processes when a single stem cell divides, onecell becomes two, one of those cells, retains itself as being a stem cell. The other one goes on and becomes you know the rest of the blood system. How does it do that? How does it make those decisions? And what is it what is coded in to those cells that say i'm a stem cell and i'm going to be able to perpetuate myself you know, forever where this other cellcan make a lot of progeny, but it's going to end up expiring. That clone will end up you know, being lost. So, we're still figuring that out today.

I think the answer to that question will help to underlie the next round of cancer therapy. But what we are beginning to learn is that these cells are wired for a number of different you know, metabolic epigeneticprocesses, and it turns out that, you know, people are discovering drugs that are trying to target these fundamental processes and some of those are coming into you know, clinical testing, clinical usage. We're learning that you know, the wiring for stress response, it's work that we've done and others. So, when i still get stressed, cells normally undergo a certain set of programs. Turns out a stem cell does that differently. It uses it a lot of that for its own survival.

Cancer harnesses some of these wiring for stress response in an inappropriate way, and that gives them survival properties. So, this leadsto vulnerabilities that are just coming into the fore now. So, i think that from the standpoint of trying to understand, what is a stem cell, what is a cancer stem cell, what is a leukemia stem cell and targeting it directly,it's still a work in progress. I mean, there are drugs. I mean, we worked onvmi one, which was a project involved in stem cell function, and others have worked on you know, a number of different you know, molecules. But it's all, i would say, early days in terms of how that goes forward.

CHRISTIAN COTÉ:
Right. Because that actually ties it to there is a what I've heard is termed a landmark discovery in 2013 involving this notion of targeted treatments. Where does this go from here, do you think?

DR. JOHN DICK:

So, again, it's the focus on drug development, what kinds ofcells you're using to test for whether a drug is effective or not, you know. So, if i have a you know, library of a thousand drugs and i just takeany old cancer cell and i expose them to these thousand drugs and i ask you know, which cells are dying twenty four hours later so that these are high throughput screens, it's being done many, many places, and you

Can have scale that to millions of compounds and so forth. But if you'reassay is which drugs here have stopped cells from growing, that's fine. That's one kind of answer. And it's important in one context. But if I'm telling you that there is a one in a million cell, that's the cell that's youknow, going to keep that cancer going for the next decade, it's going tokill you. What are its properties and how do i design assays to test a million compounds on that kind of a cell, and particularly if it's one of its properties is dormancy, how do you test you're killing a doormat cell? So, i think it's a focus on trying to re jig the whole system of discovery to focus on the individual cells of the tumor in a more focused context,

CHRISTIAN COTÉ:
over the last several years, I understand you've gone down another avenue of research, john, called the epic cohort. Can youtalk to us about the significance of that study?

DR. JOHN DICK:
yeah. So, you asked me before you know, about our studies of the cell of origin and where leukemia starts and what relevance did ithave. And we ended up moving on this line of research. I'll explain to you in a second that I never would have dreamed was even possible. And it's led us in directions that I have also never thought were possible. And that's to even thinking about something like prevention or being able to understand where leukemia starts when it starts and finding an individual during this pre leukemia phase, you know, before they walk through the clinic and are diagnosed with leukemia and actually doing something about it.

So, where did this start? Ok, so i told you at the very beginning, you know,cancer is a genetic disease. Cancer is a disease of genes that have gone wrong. But of course, that's happens in cells that have gone wrong. And so the question becomes, if in a tumor we have different kinds of cells, you know, leukemia, stem cells and other kinds of cells, are all these cells carrying the same genetic damage? In other words, are they all carrying the same burden of genes that have gone wrong? So, in the context of aml, it's interesting disease. But let's say on the day that you're diagnosed, typically we can find three, four or five genes that have gone wrong.

And so, the question then becomes is, does every cancer cell that you have in you have those same five genes or are there some cancer cells that have four of them or three of them or different combinations? And this now gets us back to Darwin right and evolution. So, one of the things that was known from the 1970s is, that of course, cancer starts ina normal cell. Cancer starts with the first hit, the first oncogene. But that first oncogene doesn't cause the cancer itself. It needs to acquire the second cancer gene and the third cancer gene. Right. You have a cellthat's picked up the first cancer gene that causes that cell potentially to grow a little bit more. Now you have more cells that have that. Now, one of those cells picks up the second cancer gene and it starts to grow even more. And you know, in the case of leukemia, it picks up the

Gene and now it grows rapidly. And and there you are. You're in the clinicbecause you're sick.

But the question is, when you pick up one gene and two genes, does that wash out the clone before or actually do they still persist? So in a cancer cell, do you find cells that have the one gene still there? The cells that have the two the three of the four, the five more of them could be the five genes altogether. But maybe there are some rare cells that still have the ancestral steps of how that tumor came. So, one of the things we were trying to figure out was where does relapse come from right? So, we know that when a person walks into the clinic, they're diagnosed. And the disease that I study aml, 80 percent of those people get chemotherapy and the disease goes away. They get put into remission.

Unfortunately, it's one of those diseases that when the next two years or so, most of the people will come back and the disease will have relapsed, that will have come back. And so, we were very interested in asking where does relapse come from? And because we can do genetics, we can sequence a tumor at relapse and sequence a tumor at diagnosis. We can begin to ask, are there genetic features of relapse which are distinct from the diagnosis? Can we take these relapse specific variantsand mind back into the diagnosis and find rare cells that might have those?

So, it goes back to our idea that we take cancer apart not as a bulk tumor cell, but we look at the individual cells of the tumor. And so, we are getting set up to do that study. And this is the early days of gene sequencing. It's called targeted sequencing. So, we had one hundred cancer genes, leukemia genes that we were tracking. This is again the early days. And the company that we're working with had made some errors in the very first panel that they had given us. So, we had run thefirst set of ten patients, got the data and we looked at the data and werealized there are some errors in it and we need to be rerun.

And the other thing was that you know, the genome center didn't have any methodology to really study this data very well. And so, my postdoc,liran slush, was looking at this data manually. Just looking at the data he’s an expert in genetics. And he was just looking at the data and he basically came across and said, you know, this works really, really well for most of the genes except for this one. And so, the need to tell you is that when you do genetic testing, you always need to have what we call a germ line control. So, what we mean is that if i'm taking your leukemia cells or taking your breast cancer cells or your brain cancer cells or whatever, and i sequence it and i find genes that have mutations in them, sometimes i don't know whether that mutation is a mutation that causes the cancer or is that a mutation that you were born with and all cells in your tissue have it?

So, what i need to know i need to compare my brain cells or my leukemiacells against some other normal tissue. And mostly what that is, is you

Spit in a tube or you do a scrape off your cheek tissue and you just have that is it's not cancer cells, it's just you. And we sequence that and we ask, well, can we find that mutation in those cells? And the answer is yes.Then we ignore it in the cancer cell because it's just you. But if it's not present in your normal tissue, but it is present in the cancer cell, then we know this is a cancer specific mutation. And so, the thing was, we weredoing this study on diagnosis relapse from a biobank. These are you know, patients who come in. Everybody can sense a little bit of their blood, gets put into a you know, liquid nitrogen and it's kept there for 10years.

And then the beauty here is that the biobank keeps samples. So, somebodycomes in, they're diagnosed, they get a blood sample taken away. And if they're one of those people who relapses two or three years later, thatgets put into the biobank tube. So, what happened was 10 years later, we went back to our clinical colleagues. Can you give us 10 cases where we have a paired sample at diagnosis and relapse? Now, that's fine, except the biobank didn't keep normal tissue and so we didn't have a germ line control. And so, this is where serendipity comes in. So, we thought to ourselves, well, ok, here's a blood sample taken at diagnosis, 80 percent of the cells are leukemia. But of course, 20 percent of the cells are normal. I mean, you know, you walk into the clinic, you have normal bloodcells. You can be rampant with leukemia, but you still have normal blood cells.

And so, we've looked at the 20 percent of the cells that were normal and we fished out the t cells because t cells are part of the immune system that are not anywhere near in relation to aml or myeloid leukemia. It's a whole different branch of the blood system. They're never implicated. They're never involved. And so, we knew if we sorted out the t cells, they never would be cancerous and they would be our normal control and sowe did that. And it worked beautifully for one hundred and two out of the hundred and three genes that we tested. Liran came to me and he said,john, there's something funny, because in four cases that happened to have this gene called the mpm 3a, the t cells were positive, very low, but they were positive. And so how could that be?

And initially we thought to ourselves, because we take a blood sample from that person, we sort out the t cells and the leukemia cells and we sequence them. Now, maybe our sorting wasn't perfect. Maybe we sorted some leukemia cells into the t cell sample and it’s just the contamination.But it turns out that that particular patient had two genes in their cancer cells mpm3a and mpm1. And so, we looked at the mpm1 gene and it was completely negative in the t cells, so it couldn't have been contamination because otherwise the leukemia cells would have had both markers in there and the t cells. And so, the only way this could have happened, the identical mutation was present in a t cell and in our leukemia cell. The only way that could have happened is if they came froma common ancestor.

In other words, there was a cell at some point in the life of that person that got that first mutation. And then over time it made t cells and over time it made aml cells. Now, the thing about our immune system is that thet cells in you and i are typically born when we were children and we stillhave the t cells that we had you know, 20 or 30 or 50 years later than we had back then. And so, we don't know what the time course was. And we also learned how long it takes leukemia to develop. All we know is there would have been a common ancestor. And so, we thought to ourselves, you know what, let's just see. Does that common ancestor still exist today in that blood sample? And i should tell you, the only time that a t cell and a myeloid cell are together is when they come from a stem cell.

In other words, the only common ancestor to those lineages would be a normal blood stem cell. And so, we thought to ourselves, you know what, let's look at that 20 percent of the blood sample that happened to be frozen away in our biobank that we know is normal. And let's sift through let's sort through the stem cells that might be present. We isolated them. We tested them genetically. And lo and behold, the normalblood stem cell, we knew that they were normal, had a mutation of this dna mp3a. So, the common ancestor that caused the leukemia was actually lying there in the blood cell of the person the day they walked into the clinic. And even more interestingly, half of that person's blood was coming from that single stem cell. So that single stem cell picked upthe mp3 mutation. It happened to expand, and it was making half of the blood of that person on that date.

And somewhere along the line, it had also become the precursor to becoming leukemia. So, what i need to tell you is that in you and i, we probably have 10,000 or even 100,000 blood stem cells that are active at any one time. So, one stem cell never makes any more than one ten thousandth of the blood system. Right. So, even if you're one stem cell was making one percent of your blood, that already would have meant that stem cell has somehow expanded and taken over and squeezed awayall the other stem cells. Here we had one stem cell that was making halfof your blood. It is squeezed away 50,000 to 100,000 other stem cells and taken over. It was still making normal blood, but by that time, it had really gone crazy.

What that told us was, oh, my gosh, we've answered two really importantquestions. We said the first oncogene, this patient is cancer cells had this gene called the mp3a. What we've said was that cancer gene must have started in a blood stem cell because we have a blood stem cell thathas it. Only that gene didn't have any other cancer genes, just that one gene. And so. We knew that the first oncogene was this gene because the patient had five of them. But we don't know which was the first one. Now, we knew it was the first one. Secondly, we knew it must have started in a stem cell. And then the other thing was, well, that didn't happen the weekbefore. The month before. That must have happened some years before. How long did that happen?

And if we would have seen that person in some screening method a year before they walked into the clinic and were diagnosed with leukemia, wewould have said, oh, my gosh, your blood stem cells have a leukemia mutation and you're destined to cause leukemia. Maybe we can do something with you.

CHRISTIAN COTÉ:
right.

DR. JOHN DICK:
and so, we thought to ourselves, how can we prove that? And maybe we have a tool to test populations of people and find people who are at risk for causing leukemia. And so, the question was, how do you do that? And so, it turns out that, you know, there are these cancer cohorts that were developed you know, many, many decades before. I mean, I'll give you one cancer cohort that we actually tested in Toronto. So, there's a colleague in Toronto named Steve Narod, and Steve was one of the people who helped discover one of the brca genes. Remember these are the genes that give you inherit them. Right. And they give you a high risk for breast cancer. And so, Steve was mining different populations of women who may be at risk for this. And there was a lot of epidemiological evidence that women of the Ashkenazi Jewish backgroundare at higher risk for carrying this brca 1 mutation.

And so, he had a thousand cases of women who had given blood to test for how many people had the brca mutation. And then he had another thousand samples of just, you know, general population samples, got his dna. We tested and we showed that about one in 50 people had our leukemia mutation in this dna sample. This is just the general population. And so, this confused us at the time because we were expecting, you know, leukemia incidence is like one in 10,000. So, we were expecting to sample a lot of people to find one person. Here all of a sudden in a thousand people, one in 50 seemed to have a leukemia mutation in their blood, and these are people who are just normal. This was the normal. These weren't the breast cancer risk or anything. This was just normal people.

And so, we need to look at bigger cohorts and we talk to our genetics colleagues in Toronto. And they basically said, you know, the largest cohort is started in Europe in the 1990s called epic, the European program in nutrition and cancer. And what they were doing was they started in the 1990s. They enrolled 550,000 Europeans across the European countries. People gave a blood sample. They filled out a questionnaire and they consented to be followed over the course of the next decades to be recontacted. They were interested in things like,you know, where do you live? How does that relate to cancer incidents?Where do you work? What do you eat? What's your bmi? And all those kinds of things are trying to figure out what is it about things we eat orwhere we live that might cause cancer and they needed a large cohort. And so, they did that. And so, it's still in operation today you know.

CHRISTIAN COTÉ:
these are typically healthy people starting off?

DR. JOHN DICK:

They're healthy people, you know, they typically run the gamut of people. The mean age is around, you know, forty eight, forty five to fifty individuals. But they range around that bell curve around that size. And so, these are people who are just healthy people. You and ifill out a questionnaire of a blood sample. And so, we went to epic and said, do you have people who got aml sometime after all is normal, but then people get disease. And so, they said, yeah, we have 100 hundred people who got aml.

And so, what we had then was their blood sample when they were normal.Right. But they ended up we knew they were going to get leukemia because that's what happened. And then we matched that with four to one. So, we had 400 cases where there are people who are matched by all criteria who over the course of twenty five year follow up have never gotten leukemia. So, these are all samples taken at enrollment. But whatwe know is what happened to them over the course of twenty five years, one group got leukemia, one group didn't get leukemia. And so then we said, can we predict in their blood sample taken years before, who's going to fall into each group? And the answer is we found it amazingly well.

So we have a very, very high predictor at identifying people who are going to get leukemia almost a decade in advance based on their normalblood cells and the kind of mutation the number of mutations can predict whether they're going to go on and get leukemia.

CHRISTIAN COTÉ:
so essentially a marker

DR. JOHN DICK:
it's a marker. So, it basically it's just marking that your blood stem cells have picked up this marker and they're starting to expand. And if they expand, that sets them up to pick up the second mutation, the third, the fourth, and then you're off the cascade. The partthat is really interesting about all this was so, so we published our paper, the original paper on the identification of normal blood stem cells in the leukemia person, the person who was diagnosed with leukemia, the 20 percent we published at the end of 2014. What that meant was that anybody who is interested in studying cancer had a lot of data on blood. And the reason for this is very simple, and that is blood was a really good normal source of tissue that's always saved from people. And so if you had colon cancer, breast cancer, you know, all different kinds of cancers, then there were big genome projects that have been going on for the last decade or so that had enrolled, you know, ten thousand people, twenty thousand people. And they always had blood control of these people and they had been sequenced.

And so, they just went back to their computers, started to look, can i find blood that actually has leukemia mutations in it? And it turns out that people could find them in their data. And so about eight or nine months later, four papers came out from top groups that basically saidwe can find leukemia mutations in the blood of normal individuals or

People who are going to get cancer for other reasons. Or, you know, i should tell you, the other dataset, which is, again, very common in genetics, was to find, you know, the genetic origins of Alzheimer's or diabetes or whatever. So, they were not not cancer patients. So, people are getting any disease, give a little bit of blood. We sequenced it. Can wefind genes that are associated with this? But what they did then was theywent back to their sequencing data and said can we find leukemia genes? And it turns out that they could. And the answer was incredibly frequently. But two percent of the time or so, one in 50 to one in 10 people, you can find people in the general population who don't have cancer. Some proportion of their blood is coming with a leukemia mutation in it. And so, they posted that, before we did our epic study.

The part that was interesting was it was age related because these studies were done just by general people being enrolled. What they showed was that you can find them below the age of 50, but by the time you're 70, 80, one in ten people actually have evidence of blood that has leukemia mutations in it. And you know, that roughly tracks with incidence of cancer as well, but the frequency is very high and much higher than the frequency of leukemia. And so, that's why we were tryingto figure out what is it? And this thing is now called chip or arch, which iscalled age related clonal hematopoiesis, clonal hematopoiesis, means a single blood stem cell, has picked up a single blood leukemia mutation, and that's caused it to compete out all the other stem cells that you have in you.

It looks like for most people that's just the normal feature of aging, doesn't cause any problem. But there's a subset and this is what we foundin the epic, was that there's this subset that we could identify because they pick up more mutations, different kinds of mutations, and that's a very, very high predictor for going on and getting leukemia. And so for the first time, we now have the possibility of even thinking about prevention in aml because we know a 10 year window, if we find people likethat to do something about, i don't know what we're going to do, but we can start to think about doing something to actually prevent that stem cell for picking up the fourth the fifth mutation and actually causing leukemia. Can we stop it before that has happened?

CHRISTIAN COTÉ:
you're listening to behind the breakthrough the podcastall 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 Coté, and we're speaking with dr. John dick, a research pioneer whose discoveries have shaped what weknow about how cancer starts and grows. His research is supported in part by the Toronto General Western Hospital Foundation, the Princess Margaret Cancer Foundation and the Mcewen stem cell institute.

John, you were born in Culross, Manitoba, about an hour west of Winnipeg, the youngest of six children raised on a Mennonite farm. And you actually went to a one room schoolhouse. By the end of high school,

I was fascinated to hear you had not taken a single class in biology. Whatwas it in this environment growing up that inspired you to pursue a career in science?

DR. JOHN DICK:
yeah. Culross, a two elevator town. Two elevators and onestore.

I had been asked that question more than once. I mean, first of all, my dadalways instilled in us kids that he didn't want any of us to be farmers. He said this is just too hard a life, get an education and do something else with your life. So, you know, that was part of the family background of adrive to get an education. But, you know, I think the other thing I mean, probably one of the biggest influence was so I'm the youngest of six and there's a big age gap between me and the rest of my siblings. And so I was almost raised as an only child.

And so, i had a lot of time to myself and I just poked around, took things apart, you know, broken engines, took them apart. I was all I guess I was acurious kid and I had unlimited opportunity to just tinker. My dad you know, gave me pretty wide autonomy to just poke around the garage andtake things apart and so forth. So, I became interested in just how thingsworked. And I suppose that curiosity is what has in some ways driven you know, our research, because, you know, there's two impetus for research. You know, one of them is you want to do you want to do good. Imean, we're doing medical research.

Cancer is a devastating disease. We're all touched by it. And, you know, I spent the first half of my career, not half, but almost half of my career,at the hospital for sick children. And every day I had to walk through thewards just the way our lab was, where the kids who had leukemia were. Right. You see those kids around and it focuses the mind to know that this isn't just an interesting problem that needs to be solved, but there is a need for it. And as we grow older, you know, more and more family are touched by this disease. So that definitely is a big part of it. But, you know, the other part I have to say is that it's, it's just an interesting puzzle. It's a bit like peeling layers of an onion. There's always another layer to peel off. And that is the intriguing part of what drives research.

CHRISTIAN COTÉ:

I'm curious to the Mcculloch legacy in terms of shaping you are influencing you. You know, in many ways you carry on their work.I'm curious what that means to you?

DR. JOHN DICK:

so, I'm the second generation, right. So, you know, Bernstein, Philips and some of my current colleagues, Norman iscoveand others where there where they're direct students. So, i'm the postdoc of one of them. So, I'm you know, a couple of generations removed now. But, you know, i often say that when we made our first finding of putting human cells on a mouse, honestly, if i really look atwhat we did in the next 10 years, maybe the next 20 years, honestly, we

Never did anything particularly creative. All we did was we kind of tooktheir papers and redid their studies but did it in the human system.

They set the framework that we could follow in terms of how you do your assays, how you interpret them, what you take from them and so forth. So, i think that that legacy you know, continues on in many, manyways. It's a real honor, i would say, to be, you know, one of the people who's been able to carry on their approach and to take it to you know, new levels, to take it to other levels.

Absolutely. And i think the other thing is the real leaders of the time, so, till, Mcculloch and semenovich. Lev semenovich was the other you know real towering giant. Now, by the time I arrived, looks at the hospital for sick children. You know, lev ceded a lot of research institutes, but he's also, you know, the father of modern medical research in Canada, actually with a number of people that he trained and the things he did. But but that that group of three set an incredible legacy and beyond thescience. But what they did was they created an environment of research,of of interaction, of collaboration, where the idea was paramount.

They didn't set up a lot of internal competitions between people. And what that meant was that people could be open with each other. Right. Soideas were prime. And so, what we have in Toronto then continues to this day, I think, is really an environment where people rather collaborate than compete. And what that does is it allows an openness because it means that my students can go and talk to anybody in any lab. We can have people come to our lab and there's no you know, deep ownership. You know, this is my stuff. You can't really look into it, right, until I get all the glory of this work. They really set the stage of collaboration. And i think that if there's almost anything that i take out of that time that I got from Alan and bob in their direct training to me is to try to create that kind of an environment of openness, because that's that's how science moves forward.

CHRISTIAN COTÉ:
and what's your approach to mentorship?

DR. JOHN DICK:

I don’t know if I have an approach to mentorship?

CHRISTIAN COTÉ:

well you won an award for it a couple of years ago, the
Mentor award and basic science. So, you must have some kind of system?

DR. JOHN DICK:
i guess it's a way of working. It's a way of working well enough to tell the trainees in the lab is that my job is to provide the right soil. Right. So, everybody comes into my group is like a plant. And some people do best if they're just left alone. Right. They it's our soil andthey just thrive because they can just apply all their independence and creativity.

And there's other people who need a lot of nurturing, a lot of watering to get to their flourishing place. It's my job is to figure out what kind of a person you are and to give you

the kind of environment. I guess perhaps what that really speaks to is the individualistic approach and the approach that i want to drive people towards independence, which means mostly leaving them alone. So you know, my job is to give them money to do the research that they can and the kind of broad guidance and challenge ideas to create an environment where everybody comes in with their own talents and so forth, but nobody knows exactly what they want to do or where they're going or what data means.

You can get data, but what does it mean? We throw that into a crucible and it's like, you know, what rises out is the phoenix, right? Everybody throws in their own thing. But what comes out is something more than what any one person is throwing in. And so, it's this crucible of ideas. Andmost of the advances that we've had in our group have not come from targeted or planned research. Yes, there's some directional let's do thisexperiment because it follows from that experiment and the methodological way of going forward. But at the end of the day, there's always the serendipitous findings. You know, the oh, why is the t cell positive here? Oh, well, maybe that, you know, it's taken us a while to figure out a common ancestor. Oh, well, you know, how do we go from here to here to here that it's taking the brainstorming of many, many people?

We also have this thing called the bear pit. If we have a top paper that comes out, you write it with the postdoc. I work on it with a trainee, but then we give it to everybody in the lab. And, you know, we basically say, let's tear this paper apart here like bears in the bear pit before we send it out to the journals and have reviewers do it for us. And what often comes out of that is we think we created the best paper, the most goldengem of a story, and the people look at it and tear it apart. But what comes out of that is new thinking, new approach. This paper means more than what your data is actually telling you or there's more insight into the data. And that only comes from people brainstorming and bringing their own ideas that then get honed and formed by interaction with yourother colleagues. Right. And so, to create that kind of crucible, i think isthe best kind of environment because it creates independence and and seeing where novelty comes in, advances how new science gets developed.

CHRISTIAN COTÉ:
you know, it's interesting when I look at your body of work and I don't know if I'm overstepping, but it seems like you hit a home run practically every time you set your mind to a problem. Have you everexperienced failure?

DR. JOHN DICK:
my, my PhD was was just a lesson in failure. Right. It it was areally, really tough PhD. And what i learned my PhD was fortitude, working on a project for months and months and months, coming in on a Monday morning, reading out the data and realizing that it all failed and on Tuesday morning had to start all over again.

CHRISTIAN COTÉ:

Because we're not taught how to deal with failure. Howdo you navigate challenges and setbacks and dead ends?

DR. JOHN DICK:

part of it is patience in some ways, you know, there's no baddata, everybody has a hypothesis. You set up your experiment to get a result and you don't get the result that you anticipate. And you do it again and you don't get the result you anticipate and you do it again. So, on the one hand, you know, if I put bleach in my tubes and I didn't get a result, I mean, that's one kind of answer, right?

I mean, I screwed up the wrong reagent was in there or whatever, but it was a well-designed experiment. Well, controlled. Everything works. I just didn't get the answer that I wanted. It means that my understandingof what I think is going on isn't mature enough. It's not clear enough. Butin the future, that data might be valuable and interpretable if I know more about what's going on.

So, failure you know, needs to be looked at in sort of a longer time frame. I mean, yes, it's clear that there are some directions of experiments that don't work, and particularly you invest a lot in them, particularly trainee's career that underlies that. I always try to get my trainees to have kind of a high risk, high yield project, but then kind of a lower risk, more guaranteed project that you can always fall back on. And so sometimes, in fact, many cases, the primary project that they cameto my lab said, i'm going to start this project, the ones they left with thatgot them their papers and their career are actually these side projects that turned out to be more interesting and generate more novel data than other kinds.

CHRISTIAN COTÉ:

how do you reconcile the urgency of coming up with better treatments and cures for patients with the time that sciencetakes, the research takes?

DR. JOHN DICK:

often the simplistic approach is to try to you know, targetcancers. For example, you know, when gene sequencing came forward, you know, everybody is going to sequence tumors. And that was going togive us insight into what kind of drugs you know, we could give those people. But by taking kind of a single cell approach, looking at the tumoras a community of of single cells, some are stem cells, some have these mutations or those mutations. What that leads to the idea is that tumorsare much more complex than just simple. You know, I can sequence a tumor and then give it a drug because it has a kinase mutation and I'm going to give a kinase drug.

Well, yes, but maybe the stem cell doesn't have that mutation, or it has that mutation but has another one and it can survive. So, the problem is bigger, cancer is a difficult problem and it takes time to recognize whatthe advances are you know, and to move them forward. There has been you know, remarkable advances that have come forward just in the lastyou know, 10 years, five years, the advances technology, the gene

Sequencing and the cost of it, the speed of it now being able to genetically interrogate by crispr and other methods, everything is moving you know, much faster and there is much faster progress beingmade. You know, in terms of moving basic findings into the clinic, you know, how do you reconcile the time of science with the need? I mean, itjust it spurs us on to continue to do what we need to do.

You know, I think that, you know, as I told you in my career, you know, i mean, for a large part of your career, you're building your career. You're driven by the complexity of the puzzle. But it's a scientific puzzle, I think, as I've come to realize that our research actually has importance not just to the community field, but to the broader field that has spurred on the idea that there is a necessity for us to do the work that we're doing. The field needs to hear our views you know, our research and bring it in to their thinking and their conception of their particular tumor type, for example.

And so, you know, it's one of the reasons that i you know, speak a lot around the world at different conferences, in different venues to try to, you know, get people to see how our research direction is taking, whether it has applications to to their own work, which is not to say that our thinking is static. Right. I mean, my thinking on cancer stem cellshas changed a lot over the years in terms of this being a really hard- wired state. But there's other kinds of tumors where it's a much more influenced state. The environment can influence the stem, the state of cells. And so, I'm hopefully adaptable to data. Right. I mean, science should be data driven, not based on anybody's opinion or you know, theirown ego or whatever. You should always be prepared to have your own thinking challenged and shown to be wrong with the next bit of data that comes forward.

CHRISTIAN COTÉ:
Are you hopeful in terms of, again, coming back to thepatient impacting patients?

DR. JOHN DICK:

Very hopeful. We're on the cusp of, yes, cancer is a tough problem, but but we are on the cusp, I think, of really bringing together big changes in technology that are really bearing fruit. And we're already seeing it. I mean, you know, there I mean, with immunotherapy, right. So. Taking lethal, you know, malignant melanoma, that was a death sentence and seeing that there are at least subsets of patients that arebeing, you know, really care is being transformed, whose life is being extended, you know, cure, ok, but, you know, if you can take a lethal disease and extend lifespan, quality of life for a decade or more, that's you know, that's an important thing. Rather than saying that every last cancer cell is gone from my body, but I've actually changed its impact.

These are all you know, really important advances. You know, there's adisease or actually the poster child for targeted therapy was called chronic myeloid leukemia caused by a translocation. And it causes a kinase or a gene that functions in the cell to become overactive. And a

Drug was developed for that, you know, and so it's the drug that turnedout to take this you know, really lethal disease and make it a chronic disease. If you sample those people, you can still find cancer cells in them, but they're held in check. They're held in control. And people can stay in that state for a decade or more. So that's an advance. And then, you know, you can think what the next kind of approach to try to get those last cancer cells off. So, i think, you know, the idea of a cancer cure needs to be not mitigated but needs to be sort of broadened out tothink about cancer control as well.

CHRISTIAN COTÉ:
I hope you don't mind me saying, john, you are of retirement age. You're entering your fifth decade as a researcher. Youhave four grandchildren. Have you thought at all about your legacy?

DR. JOHN DICK:

i don't know. I don't really think about legacy persay. I mean, we've a lot of interesting problems that we're working on. It's hardto imagine walking away from it. Right. And we're on that like, you know, the some of the research that I mentioned to you, the advances we've made in the last five years, thinking about prevention. We went from the very first finding to 2014 to 2019, coming up with a strategy that actuallyleads to that possibility. That's an exciting, remarkable thing. I'm surrounded by an amazing set of trainees. They're stimulating all the time. They're way smarter than I am. And it's just a charge to hear about new data going forward, to think about what the next steps might be, to work with people, to brainstorm with them as to what next steps are.

The only maddening part is to the desperate search to always get money.Researchers is a big enterprise. And the funding. I would argue that you know, perhaps our research has probably been the most impactful in thelast five years, but it's probably also been the period where it's been the most difficult to actually keep the lab funded to the extent that it has. So are our mechanisms for funding research are in a lot of strain, I would say, and that is you know, taking way too much of my time away from thinking about these other more important things. So, if there's anything that's going to prompt me to either slow down or whatever, it'sthe ever present need to keep the ship fueled with getting grants and writing grants and so forth.

CHRISTIAN COTÉ:
i think i know the answer to this. But there's an old saying,people don't buy what you do, they buy why you do it. Why? Why do you do what you do?

DR. JOHN DICK:
it goes back to what I said earlier. There is overwhelming need for this kind of research to go forward. I think it's important. I think it has value to create the next rounds of, you know, therapies andcures and approaches. But it's a really interesting puzzle. You know, i have to say, what stimulates me is equal parts of both of those. It's a remarkable thing, right? Somebody pays me a salary to follow my own nose. I can run my own lab whatever way i want. It just has to be successful. And that's a remarkable thing.

CHRISTIAN COTÉ:

Dr John Dick, award winning scientist at UHN's Princess Margaret Cancer Centre and the Mcewen stem cell institute. Thank youfor sharing your groundbreaking work with us and continued success.

DR. JOHN DICK:
thanks very much, Christian.

CHRISTIAN COTÉ:
Dr. John dick's research is made possible in part thanks togenerous donor support. If you'd like to contribute to this groundbreaking medical research, there's two websites you can visit.

www.tgwhf. That's tgwhf.ca/podcast or go to www.thepmcf. That's thepmcf.ca and click on the donate now button.

For more on the podcast, go to our website www.behindthebreakthrough.ca and let us know what you think. We'd love to hear from you. That's a wrap for this edition of behind the breakthrough, the podcast all about groundbreaking medical research and the people behind it at the university health network in Toronto, Canada's largest teaching and research hospital. I'm your host, Christian Coté, and thanks for listening.