Behind the Breakthrough Podcast - University Health Network

Season 4 - Dr. Gordon Keller

Transcript

BTB

Hello everyone and welcome to Behind the Breakthrough 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 on the podcast today we're so pleased to be joined by Dr. Gordon Keller, award winning senior scientist at UHN`s Princess Margaret Cancer Center and director of the McEwen Stem Cell Institute. Dr. Keller is a world renowned pioneer in the field of regenerative medicine. His scientific career has been dedicated to the exploration of using stem cells to repair damaged organs and regenerate growth of things such as cartilage and bone. Dr. Gordon Keller Welcome to Behind the Breakthrough.

DR. GORDON KELLER

Thank you.

BTB

If you don't mind, Gordon, could we start off with a primer on stem cells, namely, what is a stem cell? And what does it do?

DR. GORDON KELLER

Sure, of course, I think that's a good starting point. In the simplest terms, a stem cell is an immature cell with a potential to make other cell types. In addition to its ability to make other cell types, it has the potential to what we call self renew. That is to make more of itself. In this way, these cells are essentially immortal. Now, I think it's best to give you a few examples, perhaps of what types of stem cells there are, and that will help I think the audience understand of what the stem cells can really do. The best characterize the best understood stem cells are the blood forming stem cells. They are located in our bone marrow, and their primary goal throughout our life is to make blood cells. They produce blood cells throughout our life, because many of our blood cells are short lived, so they have to be replenished. These blood forming stem cells, by the way, were discovered right here in Toronto by Ernest McCulloch and Jim Till, in the early 60s, and this gave the field of stem cell biology a real boost, because we now had really, in our hands a true stem cell that we knew a little bit of how it functioned.

DR. GORDON KELLER
That is what we would call the blood forming stem cells. There are other stem cells systems in our body as well. Now the second type of stem cell, and I think the one we're going to talk more about today, are the stem cells known as pluripotent stem cells. So let me back up for a minute blood forming stem cells, their function is to make blood. These pluripotent stem cells are quite different, they can make almost any cell type in our body. These stem cells were recreated by scientists, and they are propagated exclusively in a culture dish in the laboratory. But the key distinction from the blood forming stem cells or the other stem cell systems in our body, is that they can make most cell types in the human body.

BTB

So I take it the premise, or promise, of regenerative medicine is that given many diseases occur because the cells in our body have been damaged or lost function, let's try and introduce these cells to replace or regrow those that have been lost or damaged?

DR. GORDON KELLER

That is absolutely correct. The goal of many of us now in the field of regenerative medicine is to make specific cell types. And to do exactly what you indicated, rather than replacing a whole organ, we can go in to specifically repair and regenerate those cells that are damaged within an organ.

BTB

Okay, so one more bit of sort of framing the narrative or history lesson here. Let's go back to the early 80s, as you are about to enter into your research career. At that time, my understanding is there are two major unknowns in the field. One is you can't introduce just any stem cell to the body to stimulate growth, it had to be an immature or origin stem cell that has yet to develop a specialized function before it goes on to say form blood or cartilage or an organ. And at that time, when you're entering the field, that origin stem cell had had yet to be found or isolated in humans, is that right?

DR. GORDON KELLER

This is correct. So I think what you're referring to by origin stem cell is the, what we call the pluripotent stem cell. Those are the lab grown stem cells. They were first discovered in the mouse in 1981. So it's about the time I began my postdoctoral studies here in Toronto, they were just discovered. So at the time, I was working with blood forming stem cells. So they had been discovered some two decades earlier. And there was a lot of research going on around the blood forming stem cell system.

BTB

So that pluripotent stem cell had been discovered in mice around the time you're entering the field.

DR. GORDON KELLER

Yes.

BTB

Okay. And then let's just close the loop here. The second major obstacle as you're entering the field is that this immature or pluripotent, origin stem cells, once you isolate it in humans, there was still another stumbling block - how do you coax that stem cell to mature into the particular cells that you needed in terms of replacement or regrowth be it heart, liver, bone, blood, etc. So that would have been sort of the second part of the challenge of regenerative medicine at that time when you were entering?

DR. GORDON KELLER

Absolutely. And so just to put some perspective on timeframe, the human pluripotent stem cell was not discovered until 1998. So we had a span of almost a decade and a half until we went from the mouse to the human. But your comment is applicable to both the mouse pluripotent stem cell and the human pluripotent stem cell. We spent probably 10 years working on mouse pluripotent stem cells understanding how to coax them into the different cell types before the human ones were discovered. But the time was not really wasted, because we could apply our knowledge from mouse directly to human. And that gave us a bit of a leg up on others who, who really hadn't had the same experience as we did.

BTB

Okay, and that's really going to become a large part of the focus. As we kick things off here into your research then, let's start in spring of 1983, your postdoc at the University of Toronto. After that you leave Canada for the Basel Institute for immunology in Switzerland to start your work in stem cell research. Talk to us about your focus once you landed there.

DR. GORDON KELLER

When I arrived in Basel, my big interest was in studying the blood forming stem cell that might give as I spoke earlier, that gives rise to the many different types of blood cells in our body. This was all work in the mouse. It's a great preclinical model if you want for this. And what we're trying to do at that point, is use viruses to tag these stem cells. And you could do this in a way that would uniquely mark each stem cell and that would allow us to follow them, follow their fate and follow their function once they've been transplanted back into a recipient mouse. And that gave us some understanding of their behavior, their longevity, and their remarkable potential. So that was really my beginning project in the Basel Institute for immunology.

BTB

I understand that not long after you arrived there, you've actually mentioned this in a number of stories in the past that you went to a lecture given by Dr. Rolf Kemler. Talk to us about what it was struck you about his lecture that particular day when you were there.

DR. GORDON KELLER

This is just one of those moments in a career where, where you listen to something or you hear something, and it really changes the way you think about things. And this happens all the time in science. And that's why communication and interaction is so important. Rolf had come, he was working in Freiburg, I believe, or in Tuebingen up in Germany, not far from Basel. And this was around three years after the mouse pluripotent stem cells have been discovered. And he came and gave a lecture and showed us that you could take the mouse stem cells out of their stem cell conditions, so they were no longer kept the stem cells. And they would form these large clumps of cells that would float in the culture media. And within these balls, you could see red blood cells, you could see beating heart cells, you could see blood vessel cells, you right there told you that these stem cells in a petri dish, could make other types of cells. And that really grabbed my attention. I thought, boy, this is something I could really work on. And once I finished the work with a bone marrow cells, and we switched our whole efforts to working on free flowing stem cells.

BTB

Dr. Kemler, used some visuals that also had an impact on your thinking about the potential for stem cells one day being a therapeutic benefit to the patient - talk to us about what you saw.

DR. GORDON KELLER

I think what really captured my attention and it does is for whoever comes to our lab now is the actual beating heart cells in the wall of this system of cells, you could see contracting heart cells. And we show this to visitors to the lab all the time now we make these routinely where you can take a stem cell and coax it along the way to make a beating heart cell. I think that visual for anyone who sees it is one of the most memorable.

BTB

Alright, so let's move through to 1990. The search for that pluripotent stem cell in humans continues, correct?

DR. GORDON KELLER

Yes. It continued was starting, you know, Dr. Jamie Thompson was the person who ultimately identified it that he was working on this for quite a while looking for the equivalent of the mouse pluripotent stem cell but from a human source.

BTB

At this point, you moved to a lab in the US in Denver, where you decide to commit all your efforts on the other unknown in this field that we talked about earlier. How would you coax that stem cell to mature into a particular cell that you needed for replacement regrowth? That decision would really be a turning point I understand for you talk to us about what went into your thinking there.

DR. GORDON KELLER

Right? Well, when you start a lab, and we certainly mentor our younger colleagues now you have to decide what you're going to work on. You can't do everything. And so you make the decision that this is what I'm going to focus on and you put all your efforts into that. It's the way science is done. You can have a certainly you can have a major research program and then more minor one. We went all in on pluripotent stem cells thinking that there was a great future here, and that the only way we're going to be successful is put all our efforts into really understanding what drives them forward, as you indicated, what takes a stem cell along the path to make a heart cell versus a blood cell, versus, say, an insulin producing cell? So we started that, and we started first on understanding blood, then we move to heart, and then we move to pancreas and liver as time went on.

BTB

I'm just curious then Gordon, at that moment, I'm sure you're reviewing as best you can, because not a lot of data at that time, in terms of making an informed decision, but was there a bit of a risk involved here for you?

DR. GORDON KELLER

Yeah. So it was, in fact, that's a good question, there was a big risk, because, you know, working with mouse cells in a petri dish, and coaxing them to do different things was interesting from a biological perspective. But there was clearly no clinical application until the human cells were developed. But the human cells weren't developed for another eight years. So we, we did take a risk thinking that at least, this system would help us understand early developmental processes in the mouse. But in the back of our mind, we were really hoping that someone would discover a mouse pluripotent stem cells so we could apply what we knew, to the human system. Yes, it was risky, but we decided to do it.

BTB

Okay, so you embark on this research of figuring out how to coax this pluripotent origin stem cell to become a particular cell now known as my understanding the term is differentiation. There's not much of a roadmap and the literature trail is pretty thin. How did your first attempt go in those first few years?

DR. GORDON KELLER

So when I've given now a few historical lectures, I show a slide. But what was known in 1990, about pluripotent stem cell differentiation, and it's a blank slide. It's literally a blank slide, there was almost nothing in the literature on how to drive these cells forward. So for the first few years, it was a trial and error method, we knew a couple of things we could do. And we worked around that, and clearly very frustrating because if something doesn't work, you don't know where to turn. But we kept going. And some of the breakthroughs were just luck, where we identified a reagent and another system and applied it to ours, and it worked or somebody else was looking at the cells, we are growing and applied what they knew. And it worked.

DR. GORDON KELLER

And so we went along for some years like that, and we made reasonable progress. And then we moved much more into a different stage of where we started looking at how did the embryo do this? Because essentially, essentially, what we're looking at is embryonic development in a petri dish. So the understanding of how an embryo, how blood is made, an embryo or a heart is made an embryo, or how a liver is made in an embryo really, ultimately informed us on how to do this from pluripotent stem cells in the culture dish. And so that was the transition from a more of a trial and error method to what we call a developmental biology informed approach.

BTB

I'm curious what kind of instability were you seeing in those initial attempts?

DR. GORDON KELLER

Oh, everything, everything you can imagine we still have it. But you know, you get something stable. And let's say you are making blood cells from these stem cells, and it works three times and then it stops working, then we don't know why. And then you go back to the drawing board and try and figure out well, what did we change and in some cases, it's nothing that you would think is obvious. But it can be a very, very small change that you made that you didn't even realize, that throws the system off. I think what many people don't understand is we're recreating, you know, a very sophisticated developmental processes that are very finely timed, and are tightly regulated.

DR. GORDON KELLER

And if you can imagine, we're trying to recreate this all in a petri dish with purchase reagents, with some system that's not quite well defined. So you can imagine that every time you start at a risk that not working. Now, we've learned a lot since we started this. And now we know that every detail is important, every detail about when you thaw the cells, how you thaw the cells, when you feed the cells, when you add the reagents when you take the reagents away, and even then sometimes experiments fail. That's the state of the art right now.

BTB

And I read one interview, going back to that time, where you said at the time, there was only modest interest on the part of the general scientific community and what you were doing, and there was just a handful of labs worldwide working on this issue of differentiation. I'm curious, was there a sense for you of isolation back then, or was this little community collaborative?

DR. GORDON KELLER

We certainly spoke to each other at meetings. There was our group there was probably I was in Denver at the time. There's probably a couple of groups in the States. There was a group in Japan and one in Germany that were really kind of the ones that I interact with, and then we're making progress, but

clearly I think people found it interesting and curious what we were doing. But I don't think they bought into the importance of the system. Until the day Jamie Thompson reported the production of human pluripotent stem cells. Everything changed that day.

BTB

And there was a change in your fortunes as well. So let's dive into that - you had a, you know, after these failures, these early failures and the slow progress in terms of figuring out differentiation, I understand you had a bit of an epiphany where you realize rather than trying to reinvent the wheel, you realize there is a model for this that you can adopt, that's been one for 1000s of years that serves as a guide on how to take stem cells and program them reliably into any cell type. Talk to us about that aha moment you had.

DR. GORDON KELLER

It didn't come from one day to the next, we understood that we are we understood over time that we are recreating what's happening in the embryo and the petri dish to some degree. It's called developmental biology. And we realized that there was a vast amount of information. So developmental biology is a huge, huge field. And it encompasses study of the mouse, study of the chick, study of what we call drosophila, or fruit flies, study of frogs. And if you start putting all these pieces together, what you found is that heart development isn't that different in all these organisms, and neither is blood. Now, there are some differences. But there are some commonalities. So we focused on those pathways that were conserved, thinking that that's going to help us a lot. And by and large, it did, I mean, it's really how we do all of our work now, when we want to try and make a new cell type, the first thing a trainee will do is dig into the literature and say, how do all these different models, organisms do it.

DR. GORDON KELLER

And then surprisingly, it works out exceptionally well for the human as well. But in these days, what we're talking about was still getting the mouse cells to differentiate. But that was extremely important for us to understand. So we knew for a long time, even our first papers, we could see that what was happening in the dish was really copying what happened in the early embryo. It just took us you know, time to get we're not developmental biologists. So we had to, we had to learn this all we learned as we went. And I think this is one of the real exciting things about science, you never stop learning, you're just learning new stuff, especially this type of science. As we move from lineage to lineage, the lineage, we have to learn all about the lineage, how they develop, and how do you regulate their their development.

BTB

So with this realization, you were able to finally in 1997, have this big breakthrough discovery, where you and your team are successful finally, in coaxing stem cells into becoming blood cells. Talk to us about that moment.

DR. GORDON KELLER

What we really looked at, in those stages, the very early stages of blood cell development. So for, for almost 100 years, there had been this hypothesis in the developmental biology field, that the blood cells and the blood vessel cells come from a common cell type called the hemangioblast. And that was debated for many, many years, it was almost impossible to identify in the embryo, because it happened, it developed at such an early stage, it was hypothesized that we'll develop at a very early stage where the embryo was relatively inaccessible. So we thought, what a good opportunity to take advantage of this model system where you can access the cells at any time at hourly intervals at daily intervals whenever you want. And so we were very fortunate to be able to really through a very timed approach, identify a cell that we showed, could make both blood and blood vessel cells. So the importance of that was to show how powerful the system was, and to be able to give back something if you went to the developmental biology field. Once we showed it in the dish, we could go back to the mouse embryo and showed that these cells also existed. But it was the knowledge from the stem cell system that allowed us to identify them in the mouse embryo.

BTB

And you now had a pathway to taking this immature cell and coaxing it into whatever in this case, this was to coax it into becoming a blood cell. What was your reaction to finally achieving this?

DR. GORDON KELLER

It told me two things. First, it said yes, we are studying developmental biology with this wonderful system. But it also told us that this model system had a lot more to offer than just this. If we could time things correctly. If we could understand the pathways that drive other lineages, I think, then the number of opportunities to study lineage development and developmental biology with the end goal of making functional cells was enormous.

BTB

And that was a world first I'm curious, what was the scientific community reaction to that?

DR. GORDON KELLER

So so this was a fairly small group of investigators who were really interested in early blood development if you want. And they of course, were very excited that we were able to use this system to show that such cells exist. Now, these cells per se, are not these hemangioblast, they're just represent a stage in the progression of the earlier cells to blood and vascular cells. But it just it answered an interesting developmental biology question. And again, as I said, it told us that this system has a lot of potential.

BTB

And around the same time, another turning point that you've indicated, you mentioned earlier, James Thompson's, had finally isolated the human embryonic stem cell. So in that moment, coupled with your discovery, Gordon, what did you see as the potential?

DR. GORDON KELLER

What we soon realized is all the work we had done in the mouse, we can now apply to the human cells. So what we were once dreaming about that someday we could perhaps use this information to derive human cells that would have therapeutic application almost immediately became a reality. There they were human cells, human pluripotent stem cells that we could now get to work with. And to be honest, we still work with some of the original cells that James Thompson isolated.

BTB

Okay, so since 1998, I understand your lab has pursued differentiation of human stem cells into a myriad of things: blood, heart, liver, pancreas, etc. Did that first hemangioblast last discovery in ‘97 act as a template for you?

DR. GORDON KELLER

Yeah, absolutely. It did, in the sense that it told us that if you take an approach where you have very precise timing, as I mentioned earlier, and you have a handle on the regulator's that control a specific cell type, you can identify rare cells, you can identify cells that are only present for short periods of time. And you can isolate them and drive them forward. So we apply that then that same thinking to other lineages, and one of the reasons we started on so many lineages is they informed the information from one, informed the people working on the other. So if you're not making one thing, you're probably making something else.

BTB

And then do I have this right another turning point in 2006, when Dr. Yamanaka of Japan figured out a way to create human stem cells from adult cells, it removed the ethical concerns coming from using embryonic stem cells. What did that mean for stem cell research?

DR. GORDON KELLER

That was certainly the second big breakthrough in the field. Now, you could make pluripotent stem cells from anybody. And just as a quick primer, you, what you do is you take blood cell progenitors you can take skin cells, and through the expression of four transcription factors. So you just turn on for transcription factors for a relatively short period of time, you can actually move these cells back in developmental history to where they're pluripotent as well. So suddenly, we had in front of us the ability to make patients specific stem cells, individual specific stem cells, it not only allowed us to think of

perhaps making cells that we could transplant back into a person. But it also opened the door to study disease in a culture dish.

DR. GORDON KELLER

To someone if someone has a disease that's caused by a specific genetic mutation, that mutation is captured in the postponed stem cell. And so one should be able to study the disease process in the dish if you can make the right cell in which the disease has manifested. And that work is now going on and now over the years, and it is now possible to study some disease processes in a dish. And the advantage of that, of course, if you have access to these cells to look for new drugs to treat these diseases.

BTB

And around that same time as Dr Yamanaka's discovery in 2006, you make another career pivot where you come back to Canada to head up the McEwen Stem Cell Institute in Toronto. What convinced you to move back home so to speak?

DR. GORDON KELLER

There wasn't a single thing I think part of it was, we're Canadian. My wife and I are Canadian. And we thought we would like to come back to Toronto and work in the Canadian science system if you want. And Toronto is a powerhouse at stem cell biology. And so it looked like a very attractive time to move back to Canada and to really see what we could do. And at that time, Rob and Cheryl McEwen had generously supported the building of the McEwen it was at that time called the McEwen Center for Regenerative Medicine, we've since changed the name to their McEwen Stem Cell Institute. There was support from Rob and Cheryl [McEwen], and there was just a lot of good stem cell biology. We have a lot of good colleagues here in Toronto. And that's something Canadians should be very proud of, and Torontonians should be very proud of is really the expertise in Stem Cell Biology and Regenerative Medicine that we have right here in Toronto.

BTB

What is it about Toronto and the Institute that's become so attractive?

DR. GORDON KELLER

Once you have a group of people with similar interests, with a similar expertise, it creates a very attractive environment for other young people to come and work and learn. And science is not done in isolation. And building a scientific community is challenging. And it just so happens Toronto is one of these places you can build these I mean, it certainly has and it's the last extensive biologic biomedical research community here, and that makes it all the easier. So it's been a really great place to do stem cell research.

BTB

Bring us up to date, if you don't mind, Gordon, just some of the leading projects you have on the go now at the Institute.

DR. GORDON KELLER

We're still fairly broad, although my lab has shared lineages if you want, we're now working only in heart and blood. And we also have some work on the blood vessel system or the vascular system. That's my lab. We have colleagues some that I've trained some that we've recruited. Cristina Nostro's lab, she's working on making insulin producing cells the ability to transplant the cells to treat type one diabetes. Stephanie Protze, she is working on making a specific type of cell type known as a pacemaker of the heart. And that's the idea there is to rather than to use a mechanical pacemaker we could use a biological pacemaker.

DR. GORDON KELLER

Shinichiro Ogawa is making functional liver cells from the pluripotent stem cells with a goal of developing new therapeutics to treat liver failure. And then Michael Laflamme we recruited from Seattle in 2015. He is a world's expert in transplantation of cardiomyocytes, or heart muscle cells into different model organisms into the hearts of different model organisms as a preclinical study for regenerating the heart. And so that's really our institute. It's a small number of people, but each one is dedicated to developing a new cellular therapeutic or a new therapeutics to treat disease. So in essence, it's we're all in regenerative medicine, we're all using cell therapeutic approaches for Regenerative Medicine.

BTB

And where are you at on the translational front, when it comes to transplanting these mature cells safely?

DR. GORDON KELLER

In a preclinical state, virtually all of the lineages are being tested. So probably the heart cells are the most advanced there. And this is largely the work that Michael has done Michael Laflamme, where you can show very nicely in rodent models and even in the pig, you can take these cells from a culture dish, these beating cells, put them into a heart that's been damaged as a human heart attack would damage the heart. And you can find new muscle growing, you can read muscular rise, as we would call it the damaged area of the heart. And so this was a huge step forward towards thinking that we can recapitulate this in a human. The liver cells that Shinichiro, Dr. Ogawa is making, certainly they will make some liver tissue in a dish, they will make a enough to secrete what we call albumin that you can detect in the serum.

DR. GORDON KELLER

Cristina Nostro, Dr. Nostro's work, we can take these insulin producing cells and put them into animals and find human insulin in the animals. And Dr. Protze's work shows that these cells can actually pace our heart for short periods of time in an experimental animal. And we've found now and this is where this is a project I've been working on for many, many years, that we can make something that's very close to a blood forming stem cell from these pluripotent stem cells, where we take these cells and engraft, and again, this is all done in preclinical models. And they will engraft and produce blood cells, over a period of some weeks. And so really, this is the stage we're at with many of the projects. So that's how these projects work, you first figure out how to make the cells and then the work is not over, then you have to show that they can function. And that's really where we're at with all of the projects.

BTB

And I'm sure you get asked this a lot - when do you think or do you have any sort of timeline of when any or one of these might enter into human clinical trials?

DR. GORDON KELLER

That's a good question. It's a hard one to answer for the following reasons. Firstly, one has to find the resources to support the work. And the resources one needs are and I'm talking mostly about funding here are significant to take the cells through to where you manufacture them, you test the safety and then recruit and run the clinical trial. We've partnered now so Mike Laflamme, and I along with colleagues in New York, are scientific cofounders of a company called Blue Rock Therapeutics that launched in 2016 through funding with Bayer and Versant ventures and the idea is that they would be our partners to help move these to the clinic and so their focus is cardiac heart disease and the ability to muscularize a heart.

DR. GORDON KELLER

And their second main focus is in Parkinson's disease. Now, that's not something we've done. But that's something that we felt important enough to have in the company. And so this is really, I think the way forward where you partner with a commercial firm, to help move these forward once the preclinical data are there to say this is looking very good. We look for partners or perhaps, perhaps, launch another company. I'm not certain, but you certainly need partnerships here to move this towards a clinical trial.

BTB

You're listening 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 on the podcast today we're speaking with Dr. Gordon Keller, award winning senior scientist at UHN's Princess Margaret Cancer Center, and director of the McEwen Stem Cell Institute. Dr. Keller is a world renowned pioneer in the field of regenerative medicine. Now, Gordon, you grew up on a farm near Melville, Saskatchewan, and you went to the

University of Saskatchewan for your undergrad where you said you gravitated to the biological sciences. What was the attraction for you back then?

DR. GORDON KELLER

I've always had an interest in biology. Growing up on a farm, of course, you are exposed to a lot of biology if you want we, it was a mixed farm. We had animals, we grew crops, but you just explored around as kids do. And I was always fascinated by whatever I saw, understanding how things worked. And not that I knew for sure I was going to go into science or do science as a career. But I gravitated towards taking the sciences and the biology's in undergrad. And then as I moved forward, I got more and more interested in research as a career, but I didn't actually start out thinking I was going to do research. In fact, to be honest, when I started, I really didn't know what I wanted to do.

BTB

That's not uncommon. One thing I wanted to ask you about is, even through your PhD years in Edmonton, you'd return for the summer harvest into the fall, where you go from sunup to well into the night, that prairie work ethic is that a translatable skill that has served you in your career at all?

DR. GORDON KELLER

I was able to do that in undergrad a little less often in graduate school, because graduate school demands that you're there for the summer. But certainly an undergrad we would go home every year and help out. Absolutely. And that's just to be expected. I think that's true for most farming communities at least it used to be I'm not sure it still is where the young people would go back and help on the farm. It's something you just did.

BTB

What I want to get at there Gordon is the work ethic it taught you - is that a translatable skill throughout your career?

DR. GORDON KELLER

I think so I think good work ethic we all had in those days was something that drove us forward. And you worked hard to you set a goal and you worked hard to achieve it. Even my friends who weren’t on farms, had summer jobs and had similar goals set that they wanted to achieve.

BTB

And talk to us about how mentorship helped shape or guide you over the course of your career.

DR. GORDON KELLER

The decisions I made were not based on as much facts and research as I see now the young people have I didn't know a lot of my community that went to university. And so the decisions were made based on my encounters and say before I went to Edmonton, one prof I said, Where should I go for graduate school? And he told me, I would suggest Edmonton, Winnipeg or BC and then I wrote to each of them, and Edmonton accepted me and that was it. There was there was no trips to look at universities or select schools or anything, then it was this is it. And that's what we did.

BTB

And today, what advice do you now pass on to your mentees?

DR. GORDON KELLER

Depends on what stage they're at. While this is advice for all of them, I say go to someplace where good science is being done. And do something that excites you. Make sure you have a community of excellent colleagues. But I think, really, first and foremost, you have to do something that you're passionate about. Don't do something because it's trendy. Do it because you really think this is what excites me. And this will help me make a difference. What is the contribution I can make with this type of work?

BTB

You've talked about the roadblocks and failures along the way to your breakthrough discovery. What's your approach to failure, because it's not something we're taught in school.

DR. GORDON KELLER

No, it isn't. But you certainly learn it in science. Because you know, if every experiment works that you try, the project may be a little too easy. The question may not be quite the question you want to ask because you're trying to solve the unknown. You're asking a question. You don't know the answer. You don't even know how to get there. So by definition, there's going to be failures. Now, I think the question is, how much failure can you tolerate? And at what stage do you say, well, this simply isn't working, I have to pull a plug. And those are things you have to really consider, especially in our business. If I set out to say, I'm gonna make this type of cell, or I want to make a whole organ, and after X number of years, you're getting nowhere, you'll have to, you have to rethink it. But our trainees still experience this, we routinely have projects, and it seems to almost go throughout the lab, that I'm not sure what happens, the reagent goes bad, where many people's experiments fail for a few months. I think that's good training. I think that's the real world out there in science. And if you weather those storms, you're gonna make it.

BTB

You're a pure scientist working in the lab, how do you keep patients top of mind?

DR. GORDON KELLER

Well, that was much more challenging before the human cells came online, you know, when we're working with mouse cells, or when we were working on mouse stem cells, the link to the patient was a what I learned here, will someday be applicable to the human cells, which will be applicable to the patient. We've taken that one step out, we're working with human cells, the cells we're working with are very similar to the cells you or I or anyone have in their body. So suddenly, you can see the direct application of what we're doing to a new therapeutic.

DR. GORDON KELLER

Now there are of course, steps, as we indicated, you need to make sure that cells make a difference. You got to make sure that they're safe. And then you need to move them all the way through the processes, the regulatory agencies to get a clinical trial to test them. But that's process stuff, the concept is there, I can make a beating heart cell that someday might help somebody who's got heart disease.

BTB

So I'm curious then, how do you reconcile that urgency of a patient's need, with the fact that science takes time?

DR. GORDON KELLER

What has taken a lot of time is understanding the pathways that allow us to direct these stem cells to make the different cell types. Now, a lot of that we've accomplished, I don't want anyone to think that the cells we make are absolutely perfect, because they're not, there's still more to go. But once we can start showing if we take these cells and put them into a preclinical model of human disease, and they help, I think we've come a long way. And so Blue Rock Therapeutics, has run a clinical trial on transplanting dopamine neuron cells, made from pluripotent stem cells into Parkinson's patients, there are clinical trials ongoing, where people are making insulin producing cells and transplanting them into patients. And there are clinical trials ongoing where people are making what are called retinal pigment epithelial cells, these are part of the retina that are destroyed, in macular degeneration. Those are ongoing clinical trials.

DR. GORDON KELLER

So it's happening now. It just takes time for each lineage to make it in a clinic. But I think that time, is now where you're going to see in the next decade or so, tremendous impact of stem cell biology, in the clinic.

BTB

Do you ever feel pressure in your work?

DR. GORDON KELLER

The pressure you feel is to keep your lab funded, to keep the projects going. And just to make sure the science continues, I don't feel pressure that I have to rush this forward to try and find a partner to get this into a patient, if that was what you were getting at. We feel that we're making great progress. And our ultimate goal is to understand the biology behind what would make the absolute perfect cell type to treat a patient. Really, first and foremost is what is the best cell for an indication.

BTB

There's a leadership author, Simon Sinek, who I like to quote to people, he says ‘people don't buy what you do, they buy why you do it’. Why do you do what you do, Gordon?

DR. GORDON KELLER

The real reason is it's fun. I mean, this is a great career. I mean, our students watch us and we were stressed out over granting or stressed out over getting papers funded, or papers accepted I should say, but you can get up in the morning and go to work and say I have an idea. I'm just going to try it. I can get up and go look in the lab, look in the microscope and see beating heart cells. It never gets old. It never gets old. We figured out how to do this. We figured out how to take a stem cell and make a heart cell. I can go to another microscope and see a dish full of blood cells. And I can do that every day. And I think from that perspective, we do it and most of my colleagues do the same thing. Because it's fun. It's intellectually challenging, and I think it's the best job I could have selected.

BTB

And you're at a stage in life where I would suggest most people are kicking back and enjoying retirement what keeps you going every day?

DR. GORDON KELLER

That's a good question. I think still the work with stem cells there, as I indicated, the fact that we can make all these beautiful cells, we can understand what is really one of the most fascinating aspects of biology and that's developmental biology. You can take a stem cell out of its stem cell conditions, and you can watch it every day. And the derivative cells are changing every day into something that we know, it's going to either start beating, it's either going to turn red as a red blood cell, or it's going to start secreting insulin. So the concept that we can continue to do that, I think keeps us going.

DR. GORDON KELLER

That being said, it is a career that is so much, you know, you have to put some thought into exiting it, if you want, we have trainees that we need to continue training and finish off. And you can, you know, you have to determine when you're no longer going to accept new members in the lab, so you can retire. So I'm thinking a lot about that, of course. So we have to at some point. And I think for all of us in science, the question is, when do you feel you've made a contribution that you're proud of? And when do you feel that you may not make many more contributions, and perhaps that's the time to put your feet up and call it a day?

BTB

Now, I know you're a fairly modest guy, and you've won multiple, multiple awards over the course of your career. Have you thought at all about your legacy that you're leaving?

DR. GORDON KELLER

Yeah, you know, we think about that a lot. I think anyone in science, you want to, I always talk to our trainees about this, what you really want to think about is, is the work you're doing making a difference. You know, obviously, we have to publish papers to keep going. But I always tell them, the most important thing is pick a project that you think is going to move the field forward. And that is the most satisfying thing you can achieve. And so from that perspective, I think we've done a lot in moving the field forward in understanding how to direct stem cells to different cell fates. So it's something I'm very proud of that we've achieved this and we've made our mark. And we've enabled others to follow up and improve on what we've done. That would be one aspect of a legacy.

DR. GORDON KELLER

And the second, of course, is what have your trainees done? And I'm very proud as well, of all the people we've trained, many of them have gone on to run their own labs. A number of others have gone into high positions in biotechnology. And so that's the other way you'll leave a legacy is that other people continue the work you've done, preferably your own trainees,

BTB

Dr. Gordon Keller, award winning senior scientist at UHN’s Princess Margaret Cancer Center and director of the McEwen Stem Cell Institute. Thanks so much for sharing your groundbreaking research with us and continued success.

DR. GORDON KELLER

My pleasure.

BTB

For more on Dr. Keller's work and 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 research and teaching hospital. I'm your host, Christian Coté. Thanks for listening.