eureka Featuring Michael Houghton

Dr. Michael Houghton was honored with the Nobel Prize in Physiology and Medicine this fall. Eureka asked Dr. Houghton about his career, advice to his undergraduate self, and publication experiences.

The talk of the town (or at least the University of Alberta) has been your Nobel Prize. How does it feel to finally be recognized for that work?

It feels nice. Big honor, of course, to get the Nobel. We did the work in the 80s - that was 30 years ago - it has been a long time but it is nice that I got it while I was working here because it helps the U of A, so I'm pleased about that.

Why did you pick the U of A? What drew you here, and why did you stay?

I think there were 3 reasons: one is that I wanted to work with Lorne Tyrell. I knew him from the viral hepatitis field for many years, I liked him, and he had been doing good work in Hep B and Hep C. Wherever I went I wanted to have someone I knew and trusted, so Lorne has been that person. He's been a wonderful collaborator and mentor. Number two, I wanted funding and I got that with the Canada Excellence in Research Chair. I won that grant and it's 10 million dollars – so it's a big grant. And number three, I wanted to go to a place that had a good reputation. The University of Alberta, in the field of hepatitis through Lorne and through its virologists, was well known and well respected.

What did you expect a career in academia would be like back in your undergraduate days, before you started research?

Well, my career has been a little different from most scientists. After my undergraduate degree in England, I went straight into the research wing of a large pharmaceutical company. I actually did my PhD working in the company, but I was registered as a PhD student at the University of London in England. Thereafter, I stayed in the private sector working for research labs within pharmaceutical companies in England and then in the US, so a bit unusual. When I joined the University of Alberta back in 2010, that was, in a sense, my re-entry into academia. While I've always been a researcher, the two places (the private sector and the universities) are really quite different cultures. But I think what I've been doing in Alberta is very similar to what I've been doing in industry, which is taking our current scientific knowledge and technology and seeing if you can use it to be of benefit to patients and their clinicians.

I'm very much a translational scientist. In my department, Medical Microbiology and Immunology at the U of A, it's mostly basic science trying to find out how the cell works, how the virus works, bacteria, and so forth, hoping that some of that can be applied in the future. I take information that's available now, and I think we can apply it to important diseases. For example, working with one of our distinguished professors, Jack Jhamandas, as a neurologist he sees a lot of Alzheimer's patients. We're working with him on a new approach to developing Alzheimer's drugs and

we're getting some very interesting results in his cell systems as well as animal models. In a way, working in the Li Ka Shing Applied Virology Institute is very similar to my 40 years in the private sector in the UK and the US.

As a researcher, what is the publication and peer review process like from within industry? Does it change the way that you publish papers, and do you find that different now that you're in academia "officially"?

No, it doesn't really. I have published around 300 papers, and most of that from industrial research labs. Even in the applied virology institute, where I've worked for 10 years, that's kind of an industrial setting so the only difference really is before you send your paper in. If it's important enough and could potentially translate to human health care, then you file a patent, and filing a patent usually takes 1-2 months. Once you file the patent, your invention is covered for clinical translation and commercialization and then you publish. The whole process of clinical development involving 3 testing phases costs typically around C$ 150 million. You cannot get partners to do that unless you have patent protection.

In industry, the best companies have very good researchers. They have to, otherwise they will fail. You don't just take current knowledge and apply it to disease, you have to be doing your own research. I worked at Chiron, this company in the States, for 25 years where we discovered the hepatitis C virus; I worked with really good scientists many of whom were at senior Professor levels of excellence.

From the angle of academic publishing, a lot of the time it's "publish or perish", so it becomes very individualistic. Do you think you retain that sense of individualism and pressure to publish from within industry?

No, there isn't that kind of publishing pressure in industry. The pressure is to make medical innovations and from those, commercial products. Industry essentially is funded by investors, stockholders - they want you to make money (that's why they bought your shares), so they don't care much about what you're publishing as long as you perform research that eventually leads to a medical innovation.

That said, as research scientists in industry, we all still like to publish just like academic scientists to share our progress, which is how scientific fields progress.

Do you remember your first publication experience?

Oh yeah! The characterization of the RNA polymerase from chicken oviducts. It wasn't a particularly interesting paper, but I was very proud of that first paper.

Industry is something that a lot of students here don't consider as something they could immediately transition into, so your perspective starting in industry and applying that to academia is really valuable.

I'm talking to you from my US house just outside of San Francisco, and there are a lot of world-class research universities in the Bay area. Not only for undergraduates, but for postgraduates and postdoctoral fellows and faculty – top-class Professors are heavily engaged with the pharmaceutical and Biotech industry here. In many cases, the professors start their own companies or consult for other companies. In Alberta that culture is not as prevalent but it is changing. Once Alberta has 1 or 2 major successes in medical innovation and Biotech commercialisation, that will catalyse a key industry just like it did in the Bay Area of California, San Diego and Boston. Alberta badly needs an

alternate industry and with its excellent Universities and secondaries, it can definitely foster a global Biotech presence.

This is interesting – they're very separate here and it's sometimes considered a sellout to go to industry. And yet that's not necessarily the case if you go to a place that's saturated with biotech.

That's not the case particularly in the US, UK and EU. It's not seen as a sellout but as highly desirable. If you want to be a professor in biomedicine and you want to get ahead, it's almost obligatory that you work with industry in some capacity. 50 years ago in the UK (which is where I was born and trained), they had an ivory tower mentality but that all changed in the 1980's with the emergence of monoclonal antibody technology from Cambridge University. That spawned a huge Biotech industry in Cambridge and across the rest of the UK and world.

It's an interesting point because basic scientists are often lowly funded. If there was just a little bit more communication and integration, then I could see that as being something that would take us far.

It's a very good topic – our Li Ka Shing Applied Virology Institute has been generously funded by the government of Alberta who have seen our potential in helping to advance the Biotech industry in Alberta which badly needs a new industry sector. As a result, we have a lot of collaborating principal investigators. For example, a program designed to develop a vaccine against Group A Streptococcus is being led by an adjunct professor in MMI (Dr. Michael Good). He's a global leader in that field and we're happy to sponsor some of his work. Hopefully, we'll have a clinical trial starting in Edmonton in 2021 to test his novel vaccine approach. We are also working with Professor Jack Tuszynski and Professor Khaled Barakat from the UofA as well as Professor Sergei Noskov (UCalgary) and Dr Kamlesh Sahu in our Institute who are all experts in Computation-Assisted-Drug-Discovery (CADD). This is fast becoming the new way to discover drugs including those that abrogate protein: protein interactions that have been very difficult to target in the past. We also work closely with UofA Distinguished Professor Jack Jhamandas on developing novel drugs for Alzheimer's disease and are seeing some exciting progress arising from the CADD science of Dr Kamlesh Sahu. Other exciting work is being done by Dr James Nieman and synthetic chemists in our institute who are developing potent new antivirals against human cytomegalovirus.

"Why do you do research in biomedicine? It's not really to further the hobbies of scientists, it's to make health better for the community."

If we're going to have talent retention and develop Alberta to be a place that people want to come to do biomedical research, then it sounds like something has to change.

I think funding has to increase to better enable our excellent scientists throughout Alberta and they in turn need to focus more on biomedical innovation in addition to basic research. I think Covid really is a wakeup call – it should teach the governments of the world to increase funding for infectious disease research since humans are under the constant threat of emerging viruses, parasites, and antibiotic-resistant bacteria.

Unfortunately, the current academic system is very much geared around publishing. Therefore, the research topic has to be very accessible to students and trainees; what that means is that you, as a trainee, cannot work on very difficult and uncharacterised areas of unmet medical need. And I think that's a pity. I do think students and profs need to spend a bit more time thinking about major diseases. You can't do it 100% of the time. If you had spent your PhD and your postdoc working on trying to find the Hep C virus for 7 years, you wouldn't get many papers along the

way and then your career would have suffered. I think there needs to be a better balance in the future and perhaps this can be facilitated by changes in the funding agencies who could fund more grants in difficult medical areas, unleashing young minds on the problems.

There's actually a real niche for this that can be filled- we often have these pillars that don't communicate. Actively reaching out and bridging those gaps is what's missing in translatability – you're right that we live in these little silos and it's industry, basic science, or clinic – they don't communicate.

"I'm still as motivated as much as I was 50 years ago, just older and more fatigued, but hopefully wiser."

You're dead right, everyone tends to be in their own silo. We need clinicians working actively with basic and translational scientists taking up challenges in unsolved diseases (there are so many) and being facilitated by new incentives from the funding agencies.

I think in the United States and UK, the funding agencies have become a lot more translational in intent. In other words, they want to see even the basic science grants having more of a potential medical and societal output, which I think is good. It's true that if you look at the Nobels awarded this year for the Crispr- Cas9 system, there was no medical ambition originally in this research. It was curiosity - and basic research - driven but will enable many major medical breakthroughs, so basic research must continue. But overall, a better balance of basic and translational science
would better serve society's needs, I feel.

I think we need to foster an interdisciplinary approach to disease in our young researchers: To think not just about your own research problems, but how other people in different disciplines can contribute to it and how you can interest other people in it.

We are part of an interdisciplinary NIH grant on the Hep C vaccine, and we just got news of obtaining a good review score that is in the fundable range. In the US, the NIH have a program where they're going to fund 40 million dollars of research on Hep C vaccines. And they're going to give four 10 million dollar grants to different interdisciplinary teams from multiple sites. There's a reasonable chance we'll be part of one of those grants. I have applied for similar grants to Canadian funding agencies without success, which is disappointing since we are one of the global leaders in this particular field.

What do you think CIHR and Canadian granting agencies as a whole could learn from what you value about the American system?

What you hear from CIHR is 'We spend a lot of money. We spend a billion dollars on research every year'. And they do. But only one of those pillars is on biomedical research – there should be more emphasis on basic and translational biomedical research from CIHR in my opinion and as Covid-19 has taught us, more funding should be applied to infectious disease research. Canada has a fine cadre of biomedical scientists limited only by funding.

"Anticipate what's going to be big in ten years time and plot your career around that."

I'd like to take you back in time to your beginnings as a scientist. Was your motivation in your early career the same as today, or have your drivers to do science changed?

My attitude hasn't changed in the 50 years I've been doing medical research. I'm still very motivated to contribute to medical research and make innovations to help patients. I'm still as motivated as much as I was 50 years ago, just a little older and more fatigued, but hopefully wiser.

It seems you were very convicted in your career early on, especially if your motivations haven't changed at all since the beginning. Was there a driving moment for you that made you want to approach science the way that you have?

Whenever I was coming downstairs from chemistry lessons at high school, I would always stop and look into the biology lab to see what they were doing. So, I had this innate interest in biology - in the processes of life. Later, thinking about what I wanted to do when I was going to study at university, I spent a week in the local library investigating various careers. They had a small room of career listings from A to Z; I spent a week just going through systematically reading all of the books in that room. When I got to M – Microbiology – I read about Louis Pasteur and I thought 'Wow, this is fantastic. This is what I want to do'. That was a very important moment. Until that point, I had studied physics, chemistry, and math – then I decided to study biology at University. Pasteur's life and his work were strong motivators for me, and I took a little bit of an unusual route joining industry so quickly. And yeah, I still feel the same way. There are so many diseases that we know so little about, let alone have therapies for, and I don't think that's right. I think we've got enough smart people in the world and enough money to do better against disease. I mean Multiple Sclerosis – why don't we know more about MS? ALS? Inflammatory bowel disease? Alzheimer's? Et cetera, et cetera. We're smart enough as a scientific community to be able to do better. Covid-19 vaccinology is a great example of how novel creative science can really excel, but we should be doing better in other areas of disease I feel.

When I got to M – Microbiology – I read about Louis Pasteur and I thought 'Wow, this is fantastic. This is what I want to do'.

Do you have any advice for somebody who's first starting to think about what kind of career in science they're interested in?

Well, one of my mentors many years ago – a great Prof (Richard Palmiter) at the University of Washington in Seattle – taught me a couple of things as a student. He said that you've first got to ask the right questions.

> **'What question are you trying to answer, Mike, in science?'**
> **I said 'Well, I'm trying to extract chromatin and study gene regulation** in vitro'**.**
> **'But what fundamental *question* do you have, Mike?'**

Sounds obvious, doesn't it? But when we're young, as trainees, we don't always do that. We're just following maybe what our professor is guiding us to do. Each of us has got to ask, 'What are the questions we want to address in our research and lives?'. The second piece of advice I got from Richard was: think about what field is going to be big in ten years time. Don't join a field that's already big now**.** Anticipate what's going to be big in ten years time and plot your career around that. If we all jumped into Covid vaccine research right now, it's very competitive and a lot has already been done. Try to figure out what's going to be big in ten years. Much of immunology and neurology fields are still black boxes. We still don't understand a lot about these disciplines, but we will for sure in 10-20 years.

People ask me: Why did you decide to hunt for the hepatitis C virus? And I think it was partly because of that advice Richard Palmiter gave me. I thought 'It's very difficult, a lot of people have been working on it already but without success. We don't really have the techniques available to solve it now but, maybe in the future, we can figure out a way. And then it really will be big for medicine'. Maybe that was part of it.

You said something interesting during your conversation with Dr. Brenda Hemmelgarn for the Faculty of Medicine and Dentistry about the cross-referencing of techniques between disciplines.

I didn't do as much literature research as I should have done. I've always not been good in that aspect, throughout my young career. But I would advise trainees to dedicate a morning every week reading Science and Nature and Cell, because that's really where the big inventions are published for the first time. It's so important. Technology determines what we can accomplish scientifically. It's an obvious statement but many of us don't keep up with the technologies which are growing exponentially and are hard to keep up abreast of, but it is essential we do so.

"Technology determines what we can accomplish scientifically."

As a senior Nobel Laureate, what advice would you give yourself as an undergraduate student?

To me, the most important thing to have as a researcher is passion for what you're doing. You've got to have a passion. You've really got to want to do it. And if you don't, find something else because it's a pretty hard life without that passion. You're scrounging around for money and grants and all that. Find your passion – it could be anything. You might want to be a ballet dancer or forester. Find out what it is that drives you, what motivates you, because if you find your passion and you work on it, you'll enjoy your life very much and you'll have a great chance of success also.

And maybe, don't be too ambitious. I was never that ambitious. All I wanted to do when I started after university was to make a contribution to medical research. It didn't have to be a big contribution – as long as it's a contribution and it doesn't matter if you actually even fail to make a contribution**.** ***As long as you're trying to make a contribution, that's the important thing.***