**PROFESSOR ROBYN WARD:**So hi there, and welcome to Research Bytes, a podcast from the Faculty of Medicine and Health which explores the work of our early and mid-career researchers. I'm Executive Dean Professor Robyn Ward, and in this episode, I'm catching up with Dr. Nick Hunt from the School of Medical Sciences, who has done some pretty amazing work on oral insulin.

And I'm very keen to hear what he's got to say about his work. But before we get started, I thought it would be great just to hear a little bit about Nick. What have you done in your career? What's taken you to this point of working on diabetes and insulin?

**DR NICK HUNT:**

A pleasure to be here and thank you very much for the invite to do this.

I've been a Sydney Uni person for a long time. So, I did my undergrad here, I did my PhD here, and aside from a brief stint over in NSW Health for about three months, I've been here for almost 10 years in research, so a good decade. So, the reason we have particularly focused on insulin and diabetes is when I finished my PhD, I jumped over from neuropathology and focused more on liver pharmacology.

And an amazing group at Anzac Research Institute as part of the Sydney Local Health District with Victoria Cogger. And the amazing team we've got together with Vic and David Le Couteur, who's the clinician of the hospital, is we started developing nanotechnology platforms for drug delivery. We were originally trying to target certain areas in the liver, called the liver sinusoidal endothelial cells, or the LSEC, and we're trying to look at how we can reverse age related changes with nanotechnology.

So, it was an incredibly fortunate time since when I finished my PhD, I got a one-year job with Vic, and then we were successful, well Vic was successful, getting an NHMRC grant. So that kind of then became the focus for us for the next three to four years, and then to kind of build on that.

So, we started off making nanotechnology platforms, and then we slowly branched into what else could we deliver with this technology. And one of the main problems facing clinicians in the hospital, as David pointed out, was the delivery of insulin if you've got a frail, older patient. One of the things that limited them from being able to go home from hospital, was that they'd have to have an initial management plan and would need someone to administer it.

So usually, it's either a nurse or you need a diabetic educator to come and instruct the family. So, we wanted something that's going to be safe and orally available. That's kind of how we morphed into the diabetes space because it's a question I do usually get, of ‘you work on nanotechnology, we have no experience in diabetes prior to 2018’, and that's how it slowly grew into it.

**PROFESSOR ROBYN WARD:**So, I mean, what I know about diabetes, what a lot of people know is that there's a lot of people in the world with diabetes, maybe close to 500 million, about say a hundred million of them are dependent on insulin. And for those people who are dependent on insulin, it's manageable when they're older.

As you say, but older people have trouble managing needles and insulin, but for a child with diabetes who is, who needs to take insulin from when they're very little, that exposes them to a lifelong exposure of insulin and and all the risks that are associated with taking insulin apart from injecting themselves forever.

So many, many decades, people have been talking about oral insulin and, and its promise and how amazing it would be. And we'll get onto the topic of hypoglycaemia soon, but, but why do you think your inventions are going to tackle this issue of oral availability, whereas many decades of work has failed to do so.

**DR NICK HUNT:**

Yeah. So, it's been something that's been around for a good 60 years, the idea of oral insulin. I mean, insulin itself was discovered over 100 years ago. We had the anniversary last year. It's an incredibly difficult area to go into and the main challenge is associated with its bioavailability and of course the costs associated with insulin.

So, insulin typically has a bioavailability of only 1 percent and we, with our technology have moved that up to 4%. So, a substantial increase but the main promise I think that we have from our technology is when we started looking at small pieces of tissue from human samples, we can get up to 40-fold more increase within the intestine of human patients, which is really exciting in an in vitro setting. We'll get to in vivo very soon.

But that's part of the challenge associated with it. As you were pointing out before, it's a combination of children that will be exposed and what we really tried to design with this technology is we pictured, if a clinician's sitting there in front of a child that's just been diagnosed, usually you do a titration series where you give them a tiny bit of insulin, see how they respond, then 15 20 minutes later, check their blood glucose, and then give them a tiny little bit more.

One of the challenges of oral insulins is they take over an hour in order to work. So, what we designed is an insulin that would work within 15 minutes, so it could be at that first point of contact, so the patient would never actually need to go into injectable needles. But it's not just on the child end, it's also on the type 2 diabetics, since that's the quite large and emerging market.

So, these are usually more elderly gentlemen, who really don't want to go on injectable insulin, so they will delay treatment for months, even a year, just to not have to do it. And if you can replace that with a tablet, it can be a lot easier, and it's also something we learned from the COVID pandemic.

People don't like taking injections at all, particularly around the vaccinations, but to be able to address that with an oral formulation can be a lot better and a better use for them.

**PROFESSOR ROBYN WARD:**

And in your paper, which I read with great interest, there's a lot of complex terminology there. And part of this series is really trying to explain some of that in lay language, or at least in scientific language that your colleagues in the faculty and elsewhere can understand.

So, you talk a lot about quantum dots, and maybe you can explain what a quantum dot is and how do you get insulin onto a quantum dot?

**DR NICK HUNT:**

Yeah, so quantum dots are an incredibly cool material, and they won the Nobel Prize for Chemistry earlier on in this year (2023).

So, quantum dots are a form of nanotechnologies. A nanotechnology is something that's between one to a hundred nanometres in size. And the usual way I get people to think about this is if you look at your finger, that's one centimetre across, you're talking about something that's a millionth the size of that.

And for another size comparison, think of the size of a soccer ball, and think of the size of the planet Earth. That's kind of the weird size dynamic that you've got. The reason why we quite like quantum dots is they exist in the realm between what is something that can't pass between the gaps in cells.

So, they can't freely move throughout your entire body, but they are something that would be quite readily cleared by certain cells that would be in your liver. So, we've been exposed to nanomaterials for eons. Any grinding material, chewing food will create some level of nanomaterial. But quantum dots are a very small formulation of that which will be taken up by certain cell types in the body, and the body's developed that technique to clear those materials. So really, we're just cheating off something that's been developing for thousands of years of how our body would usually get rid of those materials, but we're using it to be able to transport something into the body that would then be rapidly cleared out, but they could release a payload or deliver a drug at that time point before they get cleared out of the body.

**PROFESSOR ROBYN WARD:**

And how do you make one of these little quantum dots with a little insulin molecule sitting on it?

**DR NICK HUNT:**

So, it's the challenge as we slowly start moving towards translation of this tech.

So right now, we're going through manufacturing of this to good manufacturing standards. And the difficulty is, quantum dots are used quite a lot, but people would think about them, they're in their television sets. They're not something that's usually a pharmacological material. So how you do actually make them is the same process that you would for any other type of engineering material.

What we use is what is usually referred to as a hot injection method, where it really requires superheating of materials, till, effectively, if you think about a product that's been all clumped together, when you heat it a lot, it starts expanding quite quickly, and it starts, the term is nucleation, and you get separation of all these individual atoms.

And then as you slowly control how they're heated properly, they'll start forming quite complex shapes, and that's when you can start getting quantum dot formation. How you make those then, in a pharmacological setting and a biological setting, took a lot of work. But we slowly developed a process that can be implemented in a biological lab.

We did an R&D version of this, then moved on to a non GMP version, and then finally now moving to a, an accredited standard approach. So, it's required a lot of, so within the Australian context, CSIRO, who we partner for the non GMP work, was the first time they'd ever done anything like this. And it's the first-time quantum dots will be used in clinical trials for these particular purposes.

**PROFESSOR ROBYN WARD:**

And what were the big scientific challenges around using quantum dots for this purpose? What, what sort of paradigms did you need to establish, and rules you needed to break.

**DR NICK HUNT:**

Probably the chief rule is around the, the composition that we had. So, quantum dots, um, because they were designed, of course, for, for non-human purposes, uh, they've got really good versions that are not quite toxic to people.

We needed to develop a formulation that had a, a low level of toxicity associated with it. So, our ones are made up of silver and sulphur. But also start working around the idea of if you are going to be giving silver to patients, how much silver can they have? And the example I always love to give is if you're going to have our oral insulin formulation, there is more silver in a set of vegetables than there would be in that particular nanoparticle complex.

But it's a hard idea to kind of work around. Aside from that, thinking about how we kind of grow with scale component of it. So, we're, of course, used to working in a small, tiny lab, but we needed to start making gram quantities of these materials. And it's a slow process. That's quite a lot of re-evaluations at each step.

But it's had an amazing team that's kind of brought together a lot of expertise in that space. And it's great to see that we now actually are ready. to make those kinds of quantities.

**PROFESSOR ROBYN WARD:**

And one of the key advantages of, apart from being oral, is this avoidance of hypoglycaemia, which is a pretty terrible experience for any patient or a family member or a friend who's seen someone experience that, particularly in the evenings.

When I mean the evenings, I mean sleeping through the night and being hypoglycaemic is a real worry for mums and dads looking after kids with insulin dependent. So, what did you find in terms of hypoglycaemia? Is this a, an important finding for you? I mean, hypoglycaemia is the most important aspect of, of this particular technology.

**DR NICK HUNT:**

So, within Australia, there's 64,000 hypoglycaemic events each year. For those patients or even their parents, half of them will call triple zero and then ten percent of them will need to go to hospital for treatment. To be able to avoid that is incredibly important, but it's not just for the short-term complications, also for the long term.

So, the, the main energy that we're putting into a lot of diabetic management at the moment is trying to keep people in an optimal glycaemic range to try and limit the, the impact of, of nephropathy, so of retinopathy later on down in life. So, the way we went around designing this technology was to try and address that hypoglycaemic problem.

And what we aim to do is create a technology that only targets certain areas in the body. Uh, so that's where we started to target the liver. So traditionally of injectable insulin, you're giving very high non physiological dosages of insulin that will accumulate liver, muscle, and fat and almost take all the glucose out of the body instantaneously.

What we designed was technology that more closely replicated what happens physiologically of insulin. So, it's released from the pancreas, majority of it will work from the liver, and then a small amount will reach muscle and fat. What we also did with this technology is we designed a polymer that would react to its environment to control how insulins released.

So, the polymer we have is designed to be degraded by enzymes that are released in response to high blood glucose levels. So, the net effect of that is when there's no glucose within the blood, or there's very low glucose environments, you don't get the release of the insulin payload. And this is actually something we discovered around COVID vaccines, since, um, 50 percent of it will just be excreted quite freely.

Nanomaterials are quite quickly cleared from the body. And if it doesn't have a release of its payload, it just gets taken out. So, it's not going to sit around and work. 24 hours, 48 hours later, you've got something where it's either the glucose is there, it's got the enzymes to release, to release that payload, or the material is cleared out.

So that's how we get that safety component. And one of my favourite lines from this tech is we've had in mice, rats, and baboons over a thousand data points, and we couldn't induce a single hypoglycaemic episode. It's, it's great to see, uh, but you can just increase the safety profile of what insulin is. So, like, insulin typically, if you were to double the dosage, you can induce a hypoglycaemic episode.

With our technology, you need to have, uh, 20 times more. Uh, increase in the amount of insulin that you give in order to get that hypo. 2024 is the year of manufacturing and 2025 will be the year of clinical trials. Uh, so with this technology, of course, uh, we go through a traditional, um, what would it be, a commercial development process.

We've gone through and patented the technology; we then licensed it to a company and then that company is now leading it as it goes through to clinical trials.

**PROFESSOR ROBYN WARD:**

Fantastic. And I know that everyone always thinks that a lot of research takes a lot of time, which is a very true statement. It does take a lot of time.

So how long did it take you from the day you begun on this project to where you are now? How many years has that been?

**DR NICK HUNT:**

So, this has been a while. I think we originally got the grant to work on just kind of area in 2018. I've actually got a photo of the day when we actually discovered the, the polymer, because it really was a moment of, that doesn't actually look right, for how it was actually reacting in its environment.

And it turned out to be the formulation that went forward. So that was in mid 2019. What's crazy is when you go through and you're developing something for commercial translation, you can't talk about it for a long time. So, I had to sit there in conferences and people kind of go, Oh, okay, no, that's impossible.

It can't work. And I was sitting there going, we have data that already proves this. And you get there three years later and everyone's kind of going, awesome. But it's, it's a long time. So, this has taken up to, I suppose, five years for these steps. And I suppose getting it all the way through into patients and even to the phase two or phase three clinical trials, you're looking at another five years on top. Ten-year pipeline is usually how it works, and I like to think we're, we're nearing halfway.

**PROFESSOR ROBYN WARD:**

So, this is, I think, such an exciting discovery that you've made. It was really a series of discoveries, very clinically applied, addressing a really big unmet need. And it's amazing that you've been able to do this here at the University of Sydney.

And it's been fantastic talking to you today about your discoveries. And I hope that people listening out there will really be inspired by what Nick and Victoria Cogger and David Le Couteur and many other people have done to bring this to fruition and are enjoying our very first episode of Research Bytes.

Thanks for listening. You can listen back, read the paper and find the transcript on soundcloud.com /fmh-news.

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