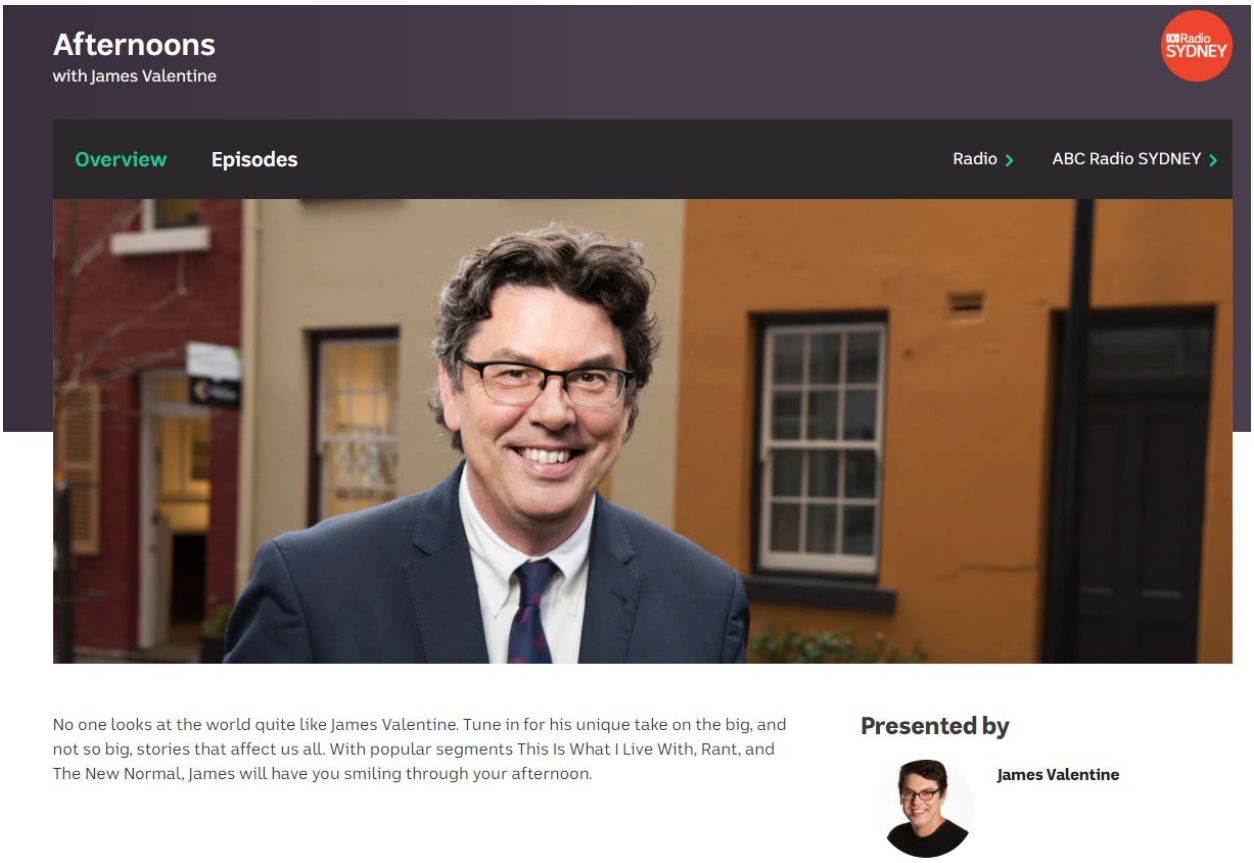

ABC Sydney Professor Roger Reddel interview with James Valentine

on August 2, 2019.

JV: The Children's Medical Research Institute is just one of the great places in Sydney and the world doing extraordinary work in genetic research. Absolutely. Cutting edge and today is Jeans for Genes Day. Because I had to say that and I'm not going to need to spell it. Jeans as in things you wear on your legs for Genes as in the things that are in your body. Jeans for Genes is a long-term fundraising awareness campaign has done terrific work bringing focus to the work of the Children's Medical Research Institute. So, we thought we'd go right to the top. Professor Roger Reddel is joining us. He's the director of the CMRI and the Sir Lorimer Dods Professor, at the Sydney Medical School, University of Sydney. He's been an illustrious doctor and medical researcher, done extraordinary work and it's great to have him in Roger Reddel. Hello.

RR: Hello, James. Nice to be here.

JV: Nice to see you. And like to remind us again, what's what's going on is the Children's Medical Research Institute get up to?

RR: Well, as you said, Jeans for Genes Day today we're celebrating all of the work that we do in genetic research. The the institute specialises in four main areas that includes embryology and birth defects.

Gene therapy, which I'm sure we'll talk about in cancer and also aspects of neuroscience, right epilepsy and diseases like that

RR: Been in place for 60 years.

JV: Yeah, yeah. What did it start as?

RR: It started with the, my namesake or the you know, the name on my University of Sydney chair, Sir Lorimer Dods. Sir Lorimer Dods was a very illustrious and quite charismatic paediatrician back in the day at the Children's Hospital when it was then at Camperdown, and he persuaded the parents of many of these patients, from various places in Sydney and throughout New South Wales and Canberra to form fundraising committees. So, it's really been fundamentally a very community oriented organisation from the very beginning was really citizens of the state.

JV: Raising funds for research.

RR: Yeah, so and we then became the first paediatric Research Institute in the country.

JV: What was the focus in 1959, what was what needed in research, then?

RR: It was very much along the lines of infectious diseases. So, a lot of the things we focused on with things like introducing vaccines against viruses and so on, which were causing serious birth defects. Rubella is something that is really very devastating if it's contracted during, you know, the wrong part of pregnancy, leading to deafness, blindness, heart defects, etc, etc. So, a lot of the focus was on things like that introduction, invention, and introduction of neonatal intensive care, development of microsurgery, things like that. And then, in the early 1980s, my predecessor as director, Professor, Peter Rowe really had a vision that the future would be about genetic research. So, he really felt that the low hanging fruit had been picked, if you like, and that the hard questions that remained would be solved by genetic research. So, we've really repivoted them.

JV: And I think this is one of the most interesting things about the Children's Medical Research Institute is that particular pivot moment, because it's so early, it's like, it feels to me like somebody in about 2005, saying, you know, electric cars are going to be go, so I'm going to 1999 it's going to be the internet.

RR: So, it was quite controversial at the time. But as it turned out, it was very prescient. Mm hmm.

JV: So, it's an extraordinary work over the years so what's the scope of it now, how big is the CRMI?

RR: I suppose CMRI is not, you know, large Institute on the, on the international scale, you know, I guess there are less than 200 people there all together. And we really pride ourselves on being cutting edge with technology and in being at the leading edge of research. So of course, that requires having researchers who've got particular expertise. So, we really focus on doing things that have unique value. We certainly function as part of big networks of researchers, both within Australia and overseas. So, there's almost nothing that we do that's done in isolation, we certainly don't want to reinvent the wheel. So, we do things with other people who have already done other things, but we really focus on doing things that nobody else is doing and adding value to the international effort.

JV: And where's your focus today?

RR: So, the focus today is in those in those four areas. But the, you know, I guess on Jeans for Genes Day, we particularly talk about the work that we're doing in genetic research and the development of gene therapy. And that's really been fueled by the enormous developments in genetic sequencing technology, which have really been quite extraordinary over the past two decades. So, what it means is that we now got the ability to diagnose with exquisite accuracy, you know, which letter or letters or, you know, small genetic defect in the 3 billion letter, genetic code, accounts for a child's you know, serious genetic illness. So that's progressed in leaps and bounds. What hasn't kept up to the same extent has been the ability to do something about it. Right. Now you have the knowledge. What are you going to do for the for the child? Yeah, we're really focused on developing gene therapy to essentially tackle the problem at its root cause. So, to repair the genetic defect in the tissues that are affected by that particular disease,

JV: Right. If we step back a little the, the point of sequencing the genome, and then the understanding of gene diagnosis there was, there was a trend for a long time ago, you've got the gene for whatever that might be, I'd be wise, you know, there's a single gene that does this. It's way more complex than that, which means that the gene therapy needs to account for that complexity as well. I meant,

RR: Yes, it is, it is very complex. There are 6000 known inherited genetic diseases. Most of them are really quite rare. So, they range from something like cystic fibrosis, which almost every one of your listeners would have heard of, which occurs in something like one in 2500, to one in 3500 Caucasians, much less common in a in Asia, for example. But that's particularly common. So, one in 25 Caucasians carries the defective gene. And it, you know, ranges from that the most common, you know, among the most common, two things that occur, one in a million or one in 10 million. Yeah. And that, you know, there is some genetic diseases where there may be only one known family in the world, right, with that particular defect. Within any one of those, there might be a whole host of different genetic changes, which result in the same, so you can have lots of different errors in the same gene right.

JV: It might not be one thing, it might be different points,

RR: There might be 13 different points in the gene defect in any one of them can result in the same end result or something very similar. So, we regard it as the same disease, but the technology to fix that may need to be tailored for each individual one of those, so it becomes quite complex.

JV: Professor Roger Reddel is with us, he's the director of the Children's Medical Research is with me, and we're talking about their most current and you know, what is always turns out to be extraordinary work, you may, you may have had some experience with this, perhaps unfortunately, you've in your family, there is a genetic disease, or you've had to seek treatment at the Children's Medical Research or being part of their research if you want to join in, they've got some experience like that to share 1300 222 2702 is our number for talk to Professor Roger Reddel this afternoon. So, tell me a little more than about gene therapy. Are you are you saying that we're at the point where we can send in the Nano bot? And do a little cut that, you know, replace the place the dodgy bit?

RR: Yes, we can.

JV: I said almost half jokingly but and you said yes, we can.

RR: Yes, so I'm very blasé about that. Because in the laboratory, so I'm a cancer researcher. In my own lab, we do that on a daily basis. So, we work with cancer cells, when we want to know what a particular gene does, we can ramp it up or ramp it down, we can put an abnormal copy in, we can put a normal copy into the cells. So, we do that on a daily basis,

JV: Are you able to describe the technology of that, you know, when we say put it in or take it out, what

RR: Where it becomes more complex is when you want to do that in a human being. So that's really quite a different order of magnitude of difficulty. Because there are safety issues. And there are also issues of scale, you know, it's one thing to be able to do these things you know, a few hundred thousand cells or a million cells in a culture dish. But if you want to correct an inherited liver disease, there are an awful lot of liver cells that you might want to correct.

JV: And what it usually be every cell in the liver, or just the one to do a particular thing.

RR: Again, it depends. So that's the answer is quite complex was it depends on the dynamics of that particular disease. In some cases, it only requires, you know, 1% of the liver cells to be corrected in order to have a very profound therapeutic effect. But there might be other circumstances where you need to do it in as many cells as possible.

JV: Right? And are you able to describe the kind of technology you are you sending some there something in there that will force the cell to change is that a physical cutting and snipping and editing.

RR: I guess I divide it into two main categories, although there are other various ways of doing this. But the two main categories are that we send in a normal copy of the gene, which is abnormal, so that it then enters the cells, it sits there, besides all of the other genes make sense, normal copy of the, of the gene product, which in most cases is a protein. And that's enough to compensate for the absence of a of a normal gene. There are some so that's, that's technically the most easy thing to do.

JV: So, it's one cell, it starts copying and hopefully wiped out the dodgy ones.

RR: So, it's it? No, no. So, it's a gene that gets sent in to each of you know, cells right into, you know, literally millions of sales. It goes in there, it sits there, it does its job. And that's enough to compensate. For the abnormal gene.

JV: A cell is small enough, but you're sending a gene, it's a tiny object. That's right, using what what's the what, what, what carries it in it, we call them vectors,

RR: We use what are essentially, viruses, which have had the words stripped out, and then we put in the material that we want to deliver to the cell. So, viruses are exquisitely developed for delivering their genetic material into your cells to make you sick. And so, we really capitalise on what they have developed to get into your cells and deliver their genetic material.

JV: That's pretty smart. Is that was that was that somebody huge intellectual leap to say, you know, the thing that we keep trying to defeat? We should use that.

RR: Yes. Yeah. I mean, it was a very fundamental insight to be able to do that. So yeah, so essentially, we strip out their innards and what we want to deliver, right? and away you go. Yeah. The other way. So instead of sending in a copy of the gene, what we can do is send in the genetic code for a word processor, right? Oh, what is, you know, functionally a word processor. So, the word processor gets

delivered to the cells. And it is able to find its way to the one in 3 billion letters. That's incorrect. And does the word processing change it to the correct one? Right. So that's more technologically challenging, but it is possible is possible. Wow. And is being done?

JV: Wow. So, there's a little it's almost like the equivalent a little 3d printer it will WordPress says it doesn't matter the analogy as such, but it's able to use our title to pinpoint the spelling of all you meant to be and put a B in there.

RR: That's right.

JV: Wow, that's pretty good as it's worth just contemplating that for a moment. That's extraordinary, isn't it?

RR: It's amazing. And, you know, I stress again, that we're doing this as part of an international effort. We haven't invented all the components. But we, are you know, contributing unique aspects.

JV: I remember when, when, when they landed the Mars Rover, you know, that the people in Houston, and stuff was saying, This is like a hole in one to Mars, it's like we hit a golf ball, we landed right on the right spot, you're doing that within the human body? That's right.

RR: Within the individual cells within the human body.

JV: Now, so what you're describing there, you're describing something that is ready to go and could be fixing some of these conditions right now?

RR: Yes and has already been done. Well, so there are conditions which are being treated by these technologies now. of the 6000. It's a very small number. But we're incredibly excited by the wins that we've had so far, right? So, we regard them as proof of principle, got to start somewhere and develop the technology for a few diseases, and then hopefully, adapt that and roll it out fora lot more.

JV: And it feels a little bit like I suppose the drug era, right, it feels like you've got the basic technology, right, and you will eventually be able to apply this to all genetic condition.

RR: Not necessarily all because some, some of them just because of the nature of you know, the way it worked was the way that some of the genetic diseases work. Some of them are going to be quite challenging to do. So, the genetic technology, I don't think we should pretend it's going to fix every one of those 6000 plus inherited diseases.

JV: Dr Roger Reddel and we're talking about the advances the extraordinary advances that are happening in genetic therapy at the moment genetic research and genetic therapy. He's the director of the Children's Medical Research at Westmead its Jeans for Genes Day.

JV: 30 years? Twenty six years. Go to jeansforgenes.org.au a, you know, you might have some questions or some experience of this, this this that you've that, you know, because perhaps unfortunately, there is a genetic condition in your family, perhaps you've had to deal with, with the Children's Research Institute, at some point, or you've got further questions. 1300 333 2702 is a number if you want to join in Roger Reddel you might like just put some headphones on there. We have a chat to Peter, who's got a question. Yes. Peter.

CALLER: James, I'm going to ask the professor with regards to epigenetics, and whether it's relevant in terms of the types of gene work that you're doing?

JV: Okay, what are epigentics.

CALLER: The idea that rather than changing the genetic structure, there are markers, and changes made through processes like methylation, which can change the way that the structures or gene aspects are switched ON or OFF, not changing the gene sequencing. All right, okay. Yep.

RR: Yes, so the epigenetics is like an additional layer of control on top of the basic code. So, you have the genome, you know, the gene, which, you know, has its instruction set. And then you've got a layer of controls on top of that, which are referred to as epigenetic. And then, of course, there are all sorts of other ways, the genes get controlled within the cell.

RR: It's quite challenging to change the epigenetics at this stage in a really precise way. Although that's being developed. There are some specific circumstances where it might be quite advantageous, just to change the epigenetic marks as a way of correcting the underlying disease. My view is that in most cases with inherited diseases, the, you know, replacing or repairing the genetic code will be most effective. But certainly, in other situations, and we haven't even touched on this. Because, you know, genetic technology, I think, is going to be very useful for treating cancer and some other diseases. There already are drugs in use that change the epigenetics within cancers, and in some cases, they can be quite effective therapies.

JV: Pretty good question. Thanks so much for joining us, Chris, what do you want to know.

CALLER TWO: Oh, Hi, thanks for taking my call. I was going to ask I mean, I thought it was so exciting when Ian Fraser came out with the concept of virus as a trigger for cancer. That was such a breakthrough discovery. Do we have any research about how many more viruses could be discovered yet? to target rare cancers to? Is there any research on this? I don't know.

RR: Yes, there's quite a lot of research on that. The evidence is that about 20% of all cancer at the moment, is the result of either viruses or bacteria. Most of the big ones, so the ones that cause lots of disease, the human papillomavirus, and as you rightly pointed out, Professor Ian Fraser was integrally involved in developing vaccines against that which we hope will prevent the majority of cervical cancers and other related you know, papillomavirus cancers. Hepatitis B and Hepatitis C are also big causes, particularly of, of liver cancer. There's a stomach bug, which is responsible for, you know, substantial proportion of gastric cancer, stomach cancers. So, it's quite well known that some big groups of cancers virally related. There are some much more rare cancers that are caused by viruses as well. And I guess the answer to your question is that we don't know what we don't know about additional viruses, which might cause other rare cancers. But people are certainly on the lookout for that.

JV: Chris, thanks for calling this afternoon, Peter, what do you want to know?

CALLER THREE: Oh, hi, James. I would like to ask the professor, just how long? I guess the treatment for gene therapy takes once the treatments been delivered, how long until it takes effect? And I guess he was put into remission? The, the problem, the genetic issue?

RR: Yep. Yeah, look, that's a really good question. And again, it's this is going to vary from a disease to disease, there is a quite spectacular example that's being worked on at the moment, there's a disease

called spinal muscular atrophy, where in the common version of the infantile form, most of the children don't leave until their second birthday. Because their major neurons are the nerve cells that control the, the major muscle groups in the body start to die off. And eventually, the children, you know, can no longer move the muscles that allow them to breathe. so devastating disease. There is now gene therapy and children in New South Wales, the first outside of North America to have been in clinical trials for this, where we hope that a single injection of a gene therapy will be curative. Now, of course, we're going to have to follow these children for a very long time to know that it gives them a completely normal lifespan. And so, we're really being very cautious as to what we're saying about the outcome. But we know that there are children who are, you know, walking now who, before the therapy wouldn't have survived.

JV: Now they're now older than two. That's, that's right. So, and is it can you go back to those children when they're 10, and take a sample of the genes and go, you haven't got up it's not there is that sort of thing.

RR: The proof is in the proof is in the walking. The proof is in the walking around, and having normal muscle function, right. So, this will be a circumstance where the gene isn't replaced. So, it's not like the nerve cells will be genetically normal, right, they'll have a normal copy of that gene, sitting beside the abnormal ones here, sitting in the same cell as normal as the abnormal one.

JV: It's, it's like, we've just found a whole brand-new tool kit, right. And then even that doesn't express the it's like we've we decided that the human body is suddenly responding to a whole different thing, you know, this is we've got so much data and information, we can now start to apply these kinds of techniques to this sort of thing. And it's, it is kind of dazzling. And you know, in the same way that we might be terrified by the aspects of the information, age and data. This is the one where we should be just incredibly excited.

RR: I think it's I think it is incredibly exciting. I mean, these ideas have been around for decades. You know, I guess quite a few people thought that this was completely science fiction. At this stage, when, for example, our gene therapy group was starting just a little over 20 years ago, working on these problems. And many of our scientific peers thought this was scientific fiction. And it was very difficult to get any sources of funding for this. So, it was really the Jeans for Genes campaign that allowed us to seed fund all of this work that has resulted in in where we are today with, you know, world leading aspects of, of gene therapy. Yeah.

JV: Well, look, you know, thank you if you're someone who's donated over the years over the last 26 years and donate again tonight. Help out Jeans for Genes. It's Jeans for Genes Day today. I've worn the black jeans today. I hope you noticed get onto jeansforgenes.org.au. get onto that website, you'll be able to find all the details about kind of things Roger has been describing extraordinary work, the Children's Medical Research Institute at Westmead and you can help out by help out by donating at jeans for jeans.org.au. Professor Roger Reddel. Thank you so much.

RR: Thank you very much, James.