

Michael Valenzuela – ‘Fixing Broken Brains’

Moderator: Welcome to the podcast series of *Raising the Bar Sydney*. *Raising the Bar* in 2016 saw 20 University of Sydney academics take their research out of the lecture theatre and into 20 bars across Sydney, all on one night.

In this podcast, you will hear Michael Valenzuela’s talk, *Fixing Broken Brains*. Enjoy the talk.

Michael Valenzuela: Thank you (0:28) and thanks everyone for coming here this evening. It’s a beautiful venue. I haven’t been here before and I’ll certainly be coming back.

Where, where to start? First of all I’ll try and outline how, how tonight will proceed. I will give a talk for about 20, 30 minutes, trying to go on a journey, really, starting with a quite tragic story and then hopefully ending up in a more positive, hopeful space. After that, we’ll just open up for question and answers and it will be literally whatever you want to ask on this topic. I will try to answer, and if I can’t answer, I’ll direct it to some of my great researchers that are here tonight. So get ready; don’t get too, too happy or inebriated.

Female Speaker: Later.

Michael Valenzuela: From what I understand, everyone had tickets to come here and those tickets were free, right?

Female Speaker: Yep.

Michael Valenzuela: So I can guarantee you’re going to get your money’s worth tonight. About four years ago I went to a dinner party. It was, it was the mum and dad of my best friend, the best friend that I grew up and went to university and medicine with. So it was myself, my wife – we’re both doctors – my mate who’s a doctor, he’s married to a doctor and his mum and dad, who are both doctors. So we had six doctors all at the parents’ home. And it was just one of those classic nights where the conversation was fantastic, lots of laughs, lots of drinks.

And I remember thinking during the night, you know, “I hope I can be like these guys in 20, 30 years’ time.” They’re still married, so that’s, that’s a good thing. They’re still enjoying and passionate about their work, even though, you know, as soon as doctors get together they start complaining and whinging. There’s so many frustrations (2:29) work. But they were still passionate. And, and besides all of that, we had a lot of common interests, especially travelling. They were about to go off to their first trip to Cuba. I had done my medical elective in Cuba. I spent three months there so there was a lot of swapping of stories. It was just one of those fantastic evenings.

Then we fast forward less than a year, maybe six months, and my mate’s mum called me up and said, you know, “Michael, there’s something I’d like to discuss with you. If you’re ... you know, you met my husband. I’ve noticed his personality’s been changing a little bit recently. What do you think about X, Y, Z?” It, it did seem to me unusual and, you know, I said, you know, “Let’s look out for a few things and get back to me in a few weeks’ time.”

We continued that conversation and unfortunately it ended up being a very aggressive type of dementia. He had been a very eminent and successful specialist. Had been still working back at that dinner party, and very intensely. And so within a year he was no longer working; he had, had to retire. Within a couple of years he needed help at home and then maybe two months ago, I went to his funeral because he had died from that very unusual and rare form of dementia.

And at his funeral, I was surprised, because I didn't know him that obviously. I obviously knew my mate very well. I was incredibly sad for him and his mum. But I was just so grief-stricken and, and I was kind of wondering to myself, "What is it about this?" and it was, "This could be me." This could be any of us. The saying, "But by the grace of God," comes to mind. And so maybe some of you have been affected by dementia in your family or your friends. It's a very common, unfortunate circumstance.

So what is dementia? Dementia essentially is, is a very simple thing. We can all diagnose it once it's at the severe end, because people can no longer recognise you. They can't remember what happened the day before, let alone a few hours ago. It's essentially when your cognitive abilities decline to the point you can't do day-to-day things: can't dress yourself, you can't eat, can't eat, you can't plan just a simple day. So that's what dementia is. It's totally a clinical phenomenon. Where it becomes complicated is: What is the cause of that dementia?

Probably the number one cause ... you may have heard of Alzheimer's disease, which is a build-up of sticky proteins in the brain. The number two cause would be vascular disease. In the same way you get vascular disease of your heart, you can get vascular disease of the brain, and that is the second most common cause of dementia. And in fact having the two things working hand-in-hand is probably the most common cause for dementia out there in the community. And then from there there is Parkinson's disease and then various less and less common causes of the dementia, so the pathology becomes less and less common. So number one is Alzheimer's and two is vascular; the combination is probably the most common, and then lots of other causes.

So let's just think about Alzheimer's disease for a second. So Alzheimer's Disease leading to dementia, the number one thing, or the first most common thing, is it becomes difficult to remember events, names, things that happen in, in your life, in your world, from moment to moment, particularly if you, if you have to go back in time and particularly if you have to go forward in time. If I have to remember, "Oh tomorrow I've got to do ... go to the hairdresser," or, "Pick up this from the shop," it becomes very, very challenging.

And so that's memory, so memory loss is the most common early form of Alzheimer, dementia. And why is that happening? It's because we have loss of brain cells in the hippocampus. So the hippocampus is this memory structure. We've got two of them very deep in the brain next to ... you know, near the ears but deep in the base of the brain. So the hippocampus is the memory centre. And so Alzheimer's disease, when it first presents itself, is essentially because of a massive loss of brain cells or neurons in the hippocampus. And it is massive.

So imagine we've got a brain structure in the hippocampus. It divides into lots and lots of little sub-structures. Just one of those sub-structures, once you've got this early form of Alzheimer's Disease, you've lost five million brain cells in that one little sub part of the hippocampus. And so if we add all of those up, in early Alzheimer's, you will have lost millions and millions of brain cells.

So if we have any hope of rectifying this or combatting it or the word “cure,” which is a dangerous word in medicine. If we’re ever going to reach that place, we’re going to have to replace millions of brain cells in the hippocampus, at this early stage, let alone the late stage where it, it rises exponentially.

So how are we going to do this? At the moment there’s lots of different strategies out there. The one that we’re trying to use and exploit is probably the most ... it’s almost like the agricultural method. You’ve lost five million cells; we’re going to put five million cells back in there. You’ve lost ten million cells; we’re going to put ten million cells back in there. So just let’s imagine, for a second, what that means, putting five, ten million cells back in the hippocampus.

Well first of all, we need a way to manufacture these cells. We need massive quantities of cells. And so for more than ten years now we’ve been working on a method to do that. And that method has to be reliable. You know, if I’m going to make this for a person, that person has to work for that person and the next person and the next person and so forth. And those cells, those millions of cells that I’m going to work with, we need to be able to predict how they are. We need a quality control system. So that’s the first step, very challenging.

The second step is that there are a myriad of different strategies to produce those cells. Some of those, the origin of those cells, could come from the same person and I think that’s an advantage because then the body is not going to reject those cells once you put it back in. If those cells originate from someone else, then you could get rejection of those cells. We, we have transplants happening every day. When they come from not the, the host, so from a donor, then we need to do immune suppression, and that’s very ... that’s a big challenge for the body, particularly for cells going into the brain.

The next step is that today, probably the most popular form or origin of cell is to get any type of cell from the patient and then genetically transform them into a cell that we can grow up. If you’ve heard about it, they’re called induced pluripotent stem cells, or iPSs. It was given to Yamanaka who got the Nobel Prize a few years ago for inventing this, this technology. It’s a great technology for studying stem cells, but it’s very difficult, from a clinical point of view, because you’ve genetically modified a cell. Now you want to put it into a patient. Those genes that you’ve mucked around with, are the same genes that make cells multiply more and more and more and more. So in other words, you’ve genetically created a cell that is very prone to becoming a tumour, because you want to put it in a brain and then it could amplify.

So ideally you need millions of cells, hopefully from the patient, not genetically modified, what next? Well we’re going to have to deliver them to the right spot. So I’ve talked about the hippocampus, different sub-structures. If you’re doing that in St Vincent’s Hospital or Prince of Wales, that’s relatively doable because you can do brain scans during the operation, so you can literally see the tip of the needle going into the brain, into the right spot. Anywhere outside of that environment is not, is not a trivial exercise.

So let’s say we’ve delivered those cells to the kind of right spot. It’s no point if those cells just ... you’ve delivered there and that’s it, they’re just a blob of cells somewhere in the hippocampus. What’s the point of that? Those cells then need to start to migrate, to move to the right places. So I may have been injected here and there’s a big empty space of lack of neurons and I’m going to have to move to that place. So that’s called migration.

So let's hope, imagine, the cells have started to migrate to the next place. Then those cells have to survive. They have to survive in a very hostile environment because this is a brain under attack. It's, it's a brain that's ... has Alzheimer's pathology all, all around it. There's dying cells all around it. So it's going to have to survive and be resilient, but not go crazy, 'cause we don't want cells that can survive and just proliferate and expand and divide in an uncontrolled fashion, 'cause then that leads to a tumour.

So we've got the cell that's been in the right spot, it's surviving, it's migrating. What next? It has to start to become brain cell, right, 'cause we've injected a, a kind of a primitive, or very childlike, cell. But this cell then has to mature into a neuron, or a brain cell, that can do something. And so that takes time.

And then finally, you've got our stem cells and they've migrated to the right spot and have become neurons, no cell, like no man, is an island. What is the point of having all of these beautiful neurons if they're not connecting with the actual brain, because that is what's going to restore the computational power of those circuits? It's going to recover the brain function. It's going to recover the person clinically. So (14:21) starts to make what are called synapses or connections between the host brain, that's still there, and the donor cells that we're introduced. And that's called synoptic integration and that's probably the most technically difficult thing to show. So that's the kind of process that we're trying to achieve.

So in our lab, we have a type of cell that has been able to do all of those things in laboratory animals. So we call them skin-derived neural precursors. I'm just going to call them skins. Why skins? We're going to have to go backwards in time now. We're going to have to go all the way back to the moment of conception. Yes, your mum and dad had sex at some point in order to create you, unless you were an IVF baby. And so at that moment, we had the sperm eating the egg, created an embryo. That embryo was one cell and then first division became two, second division became four, eight, et cetera.

So as soon as it was a little ball of maybe 60, 100 cells, already those cells start to organise in a special way. And we have the cells right in the middle, which are called endoderm. Those are the cells that are going to become our heart and our liver and the internal organs. In the middle are a bunch of cells called mesoderm and they're going to become bone and connective tissues, cartilage and so forth. And in the outer layer, called ectoderm, these are the cells that are going to become your brain and your skin.

So right back in the beginning, brain and skin came from the same place, which means all of your skin cells right now, deep, deep, deep down in their DNA, they have a memory that they could have been a brain cell. And all of your neurons, deep, deep down, have a memory that they could have been skin. And the only reason some became skin and some became neurons is because of where they were in this early embryo, the environmental cues they were getting. It's an amazing thing, as soon as you think about it. Mind blowing.

So we take advantage of that biology. So we start off with a small piece of skin, from surgery, we bring it in our lab. Tom here, he chops up that skin and then starts to put it into our recipe, and that recipe is essentially trying to give those skin cells an incredible environmental message that, "Don't be skin anymore; be brain." And that's what happens, incredibly. In a very small fraction of those cells, they start to alter what they're doing in life from being skin cells into brain cells. And so we take advantage of this and we can start to grow up millions and millions of cells.

So we can get ... from a small skin biopsy, we can end up with a million of these skins in about a month's time. We can do that time and time and time and time and time again, from dog skin. Now let's park that for a second. Don't worry about dogs.

So we've done ... we've perfected this technique in dogs. And so it's all well and good doing this in the laboratory. Our first set of key experiments was starting with those dog skin cells and injecting them into the hippocampus of old rats that had lost their memory. Old rats don't get Alzheimer's disease, they don't get dementia, but they become very bad at remembering the location of places in their environment. They get confused very easily. So we dropped in these dog skin cells into the hippocampus of these old rats and wait and see what happens.

And so when I went back ... when the first time we did this, I went and looked at these rats a few months later and I walked into the lab where the cages of the rats were, and all of a sudden the rats were up there looking at me and their tails were wagging. And I was like, "What?" No, not true. But we did, we did put them into a memory test and we showed very, very clearly that these old rats were no longer behaving like old rats in terms of memory, that their memory had gone back to that of young rats.

So this was the first proof of concept that maybe it is possible to rebuild these memory circuits through this strategy. We then looked at their brains after, after sacrifice, and we could see these transplanted cells in the hippocampus, and they no longer looked like these immature stem cells. They looked like proper neurons in a proper organisation, so that was very exciting, very exciting in the, in the dementia area.

However, we've cured – cured – Alzheimer's disease in mice or rats, 50 different, 50 different ways, 50 different times. And in none of those strategies, when we've tested them in humans, has been successful. And there's just ... the reason is, there's just too much of a difference between rats and humans, mice and men, whatever you want to think ... however you want to think about it. And so we've needed this bridging species, and this is where the dogs come in.

Ten years ago ... and the reason I got involved in dogs is I had an older dog and I took him to the vet for just some random reason. He asked me, "What do you do?" "I'm studying dementia." I was a PhD student at the time. And he said, "Do you know dogs get dementia too?" Like, "What? No. Tell me more." And that's what started a whole ten-year research area about canine dementia, doggy dementia. And it's, it's an incredible fact. Older dogs, about 10-15%, if they get old enough – so live beyond ten years – about 10-15% will get this dementia syndrome. They forget that you're their owner, so they stop wagging their tail when they see you. They'll get lost in their house. You know, if I go to a door, I know that's the way I open it, whereas a dog with dementia gets stuck in the corner near the hinge and just starts staring at, staring at the walls, start barking at night non-stop; a lot of symptoms that you can see in humans.

If you look in the brains of dogs with this dementia syndrome, you'll see the same Alzheimer pathology: massive loss of neurons, the Alzheimer pathology and other pathology. And then I looked at a brain of a dog in an MRI scan and I was stunned because they have a hippocampus like a human and a hippocampus like a rat. So this is literally a dog ... a species, that is in between rodents humans. And so that, that was, that was a done deal, I was going to look at this.

So we started a collaboration with the veterinary school at Sydney University and we can now diagnose dementia very faithfully and accurately. We have MRI protocols to image their brain and we developed this protocol to grow up skin cells from a small biopsy of an old dog.

And so finally, we kind of get to where we are today, which is the Dogs + Cells Trial. So what the Dogs + Cells Trial is, is recruiting these old demented dogs – people’s pets – usually the owner’s at the end of their tether. They’ve tried human medication, other medication, can’t manage the animal and, you know, they’re thinking about putting him down. And so what we do is we get them into our study. There’s a lot of entry criteria. A lot of dogs get eliminated because of that reason. Those that meet our criteria, we get a skin sample from this demented dog. It goes to Tom. We grow up a million, two million of these cells. And on a particular day, we have the MRI scan of that dog and we deliver a million of that dog’s skin cells into its hippocampus and a human neurosurgeon does the neurosurgery and they recover and we follow them and see what happens.

We’ve done this three times now and I’ll talk a little bit about each of those outcomes, after a brief break. So Dogs + Cells Trial: Our first patient was Sasha. Sasha was a 12-year old Kelpie/Blue Heeler. She was a beautiful dog in terms of her nature, you know still was a friendly dog, just didn’t know why she’s being friendly. You know, just good-natured. Get lost all the time, classic canine dementia presentation, pretty sick in terms of general health. It was a borderline call as to whether or not we should go ahead with the surgery; we decided we would. The surgery went fine and we were high-fiving each other because it was the first time we did it. It was a ... so many things, so many ducks to line up.

And then I went home and in the middle of the night the research assistant called me, “She’s having seizures.” We controlled the seizures. She was in hospital for an extended stay then got discharged home and then we were waiting and seeing with our fingers crossed. Unfortunately for Sasha, she had a pre-existing issue of bad kidneys, and the whole stress of the surgery, plus the seizures, means she wasn’t drinking well. Things spiralled and she had to be put down about two to three weeks after the surgery.

Pretty devastating. Our first patient. We all got really like emotionally connected with Sasha and that night, when I took Sasha’s brain out, it was one of those very poignant moments because this was not an anonymous rat; this was an animal that someone had loved and we’d cared for. And you know, it was one of those moments where you think whether to push on or not, but we did, and that led to Timmy, Timmy the wonder dog.

So Timmy is a Cocker Spaniel, 13-year old. Also has these wandering, disorientated issues. Was living in a household where they had other dogs, younger dogs. They used to really get along but now Timmy was isolating himself, not engaging with the dogs or with the owners or with the kids. And his number one problem, which was driving everyone batty, was his day/night cycle basically swapped. So he would be doing nothing, zoning out all day, and then would wake up in the middle of the night and be barking, essentially, and urinating in the house. Disaster. No one was sleeping.

And so Timmy came into our trial and this was more than a year ago now. At the three-month time point, Timmy’s score on the, on the way we rate dementia, which had been in the 80’s ... so if 50 is diagnostic ... sorry, in the 60’s. He was definitely over the threshold. He was now in the 30’s. So he was behaving like a normal older dog. All that barking and, and, and, and urinating around the house had been fixed.

So now Timmy would get up once or twice in the night and he would go to his doggy door, do his business outside, come back, find his bed and everything was amazing. So the owners got Timmy back. He's now one year post his operation and still functionally cured, behaviourally cured. So that was an amazing thing to be involved with.

And then next came Leo. Now Leo's story is the kind of story you couldn't, you couldn't write the script for. So Leo is a little thing, a terrier-type number. He is also ... they're all in the same age, 13 years of age. Leo's profession, his working life, had been as a dementia carer dog. So Leo would visit the nursing homes around Sydney and the, the older people with dementia would basically feel better by seeing Leo, patting Leo. He had a very friendly nature. That's what he did for a living. And then Leo gets dementia.

And Leo, again, gets all of the symptoms, but the thing that was very distressing is that his number one thing was just spontaneous aggression. And you know, he'd be one moment chilling out or zoned out, the next day he's growling at the owners and trying to snap at the kids' feet. And we've got video of the owners with a broom trying to, you know, push Leo into the cupboard or something until he, until he gets back to normal.

So we treated Leo in February of this year and again, at first, no big change. A few weeks later, things are starting to calm down. And around that three-month time point, we do our tests, and Leo had gone, again, from the 60's, you know, to 30, and the aggression had gone from every day or every two days to once a month to hadn't occurred for at least a month. And, and Leo's been from then ... so he's now six months, seven months post-operation. Had a little flare-up of his aggression but that's gone back down to being completely manageable. And again, we've got vision of Leo not just being aimless, but really being a nice little dog. So he jumps on your lap, wants to be patted, even remembering his commands - you know, stop, sit, stay - which he'd just completely lost.

So Leo is our second successful patient, where we've gone from a bit of skin that wasn't doing much useful, into the lab, we've grown it up, we've delivered it to the hippocampus under the right conditions. And through the miracle of the stem cell biology, these cells have survived, they have migrated, they have connected into the rest of the brain and led to recovery of memory and other cognitive function. So I think there is hope. I think there is hope that these positive results continue in our dogs. And if that occurs, that we can then move to human clinical trial very quickly.

So that is our story about Timmy the wonder dog. I hope you've found it interesting. And now we'll move to questions and answers. Thank you.

Moderator: Thank you for listening to the podcast series of *Raising the Bar Sydney*. If you want to hear more *Raising the Bar* talks, head to raisingthebarsydney.com.au.

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