

SANDRA COOPER:

Good evening, everyone. It's lovely to be here. Before we begin, I would like to acknowledge and pay respect to the traditional owners of this land, the Gadigal People of the Eora Nation on which lands the University of Sydney is built. As we pay our respects and learn lessons from the knowledge imparted from Aboriginal Custodianship of Country.

Welcome to you all. It is a wonderful turnout. Monkol and I were interested to hear what has brought you out from your lives to hear us this evening. It is not about us asking questions of you.

I am Professor Sandra Cooper, I am a professor at the Sydney Medical School and I work at the Children's Hospital at Westmead. It gives me great pleasure to welcome Monkol Lek back to the university grounds.

I have known Monkol for 10 years since he and his wife Angela came and did their PhDs with us and our team at the Children's Hospital at Westmead, studying genetic causes of inherited nerve and muscle disorders.

Monkol is born in Cambodia. He came to Australia when he was 18 months of age. He went to Seven Hills West Public School And Blacktown West High School. And then he has done three different undergraduate degrees and a PhD. So he clearly has a few wires short.

Monkol, I'm going to pass over to you to talk about three stories tonight – what brought you to the stage today. Welcome.

(Applause)

MONKOL LEK:

Thank you very much, Sandra, for the very kind introduction and generous comments. And thank you to the audience for giving up your Monday night to be here. It is a fantastic turnout.

So, I am really delighted to be here, back at home. I arrived yesterday, so I'm not thinking about the time difference on the east coast. I am honoured to be here at the University of Sydney, where I did my PhD.

The title of my talk is 'Taking Control of our Genetic Destiny'. And I mean this in two levels. One is taking control and trying to understand what is causing genetic disease in rare disease patients, and on another level, now we have all these exciting new genetic technologies is taking control in terms of knowing exactly what is causing our disease and translating this to therapy – something we have not been able to do until the last few years, to actually be truly personalised.

I am going to give you three stories of patients – one, my own personal diagnostic odyssey. The second is a family in Australia that was the first family we sequenced when I arrived in Boston, at the Broad Institute, to work on neuromuscular disease. And the last one is the story of another patient and the focus on some of the research we're doing at Yale University.

First of all, I am very nostalgic, I always think about, when I was last in a particular place. So I'm thinking when was I last at the University of Sydney. And the last time I was here was at my graduation in 2012. It was a special day because here is the professor and this was her last university event, where she also gave the talk at my graduation before she became the director at the Murdoch Children's Hospital.

It is also special because my current boss in Boston also came along, who is also a University of Sydney alumni and a former student. It was special to have that graduation with all of my fellow PhD students, who finished at the same time, as well as my wife. So it made it a special day when I was here. And it was a very sunny day, as you can see. 2012, so not too long ago, in terms of my life.

I'm going to tell you, on the first journey, this is my journey as a rare disease patient. This is me talking as a patient rather than a researcher.

This was taken in Bankstown. I'm not sure if this fountain is still there. This was taken in the 1980s, with my brother. My family, when I was a baby, around 18 months old, arrived in Australia as refugees from Cambodia. We were fleeing the Khmer Rouge and what was happening internally in our country.

I was the youngest of the children. For your convenience, I have labelled all the family members, including my mum and dad, and this is me, the youngest of seven children. And for those with much better eyesight than me, you will notice there is a pattern with the birthdays, 4/5, 6/7... You can see that the pattern starts on the first of the first, if I was the youngest of seven.

And I'm just grateful that the Australian immigration officer had a much better sense of humour than the American immigration officer and he looked at my mum and thought, "Wow, you are good with your timing."

My birthday was changed to 10 April because my parents knew when I was born relative to the Cambodian New Year. Unfortunately, all our paperwork was burned in the time of the Khmer Rouge and birthdays were not a big thing in Southeast Asia.

So we arrived in Southeast Asia and one of the suburbs I grew up in his Bankstown. So I learned to enjoy Australian sports such as cricket, rugby league, and I have always been a fan of the Canterbury Bankstown Bulldogs ever since. Unfortunately, they are not going through good times at the moment.

Also, when I was 10 years old, we moved to live in Blacktown, where I went to Seven Hills West and then Blacktown Boys High School. Living in working class suburbs in Western Sydney, I learned to not take things for granted and truly cherish all the good things that happen in both my family's life and my life.

And so growing up in such a big family, one thing you learn is, learn to share. But now, looking back, sharing, to me, was a little bit overrated.

The other thing you learn is how to eat and enjoy rice, and not the thing that goes with the rice, as we only had one income-earner, which was my dad. We had a very small and modest living.

So when I was 10 years old, my sister got diagnosed with a muscle disease. They thought it was genetic, because my parents didn't have it but they were thought to be carriers of the disease. That means they had one defective copy of the gene.

With recessive diseases, that means that each one of my siblings had a 50% chance of inheriting one defective copy, and they would just be carriers and unaffected. So they still have one functional copy to create that muscle protein. While they had a 25% chance of getting two normal copies and my sister and I got the bad end of the stick. We were the remaining 25% chance and got two

defective copies and we couldn't produce the muscle protein.

But at the time I didn't know this. Because this was the late '80s and there was only one disease gene known for muscular dystrophy. So even if we did know, it is hard to screen. So I didn't know my genetic destiny to develop a muscle disease because my muscles were normal functioning at the time. I was able to enjoy a relatively normal childhood.

It was not until I was 19 that I started realising. This is towards the end of my first university degree, that I started noticing that my muscles were sore. So I would take public transport from Blacktown to Central Station and from Central, a bus to Kensington to the University of New South Wales. So it was about 1.5 hours there and back. I would come home absolutely exhausted.

I was too exhausted to study. So I also noticed at the train station I found it difficult to go up stairs, and just keeping balance also, when I was nudged or on uneven surfaces.

As a young man, you always think, maybe I'm just having a bad week, this will go away. But as it started getting worse, I couldn't keep ignoring it. I went from doctor to doctor until one doctor did a blood test.

What he was testing for was this protein, creatine kinase, that leaks into your blood, when your muscles are damaged, it leaks into your blood. My levels were quite high that he would say, did you run a marathon or do something athletic and I said not at all. So he said, there must be something seriously wrong with your muscles because it is showing muscle damage.

From there, I got a diagnosis and gave a muscle biopsy. One of the reasons I delayed giving the biopsy is that it really hurt. I thought it would hurt, and it really did hurt.

At the time, because our genetic diagnosis wasn't too fantastic, looking at proteins and muscle biopsies was a way of looking at clues for what was actually causing a disease of TCAP that was causing a rare version of limb girdle muscular dystrophy, type II.

This is through the hard work of the researchers in the University of Sydney based at the Westmead Children's Hospital. It was led by Dr Nigel Clark and Dr Leigh Waddell, who would go down each one of those rabbit holes until they eventually found it. So I was incredibly grateful.

One of the reasons I went to the University of Sydney and the Westmead Children's Hospital, because at the time I didn't have a genetic diagnosis, the tip was, if you want people to work on your disease, just be there every day.

So I was that person they would see in the hallway every day. I never asked them to find something, but yeah.

And this was presented as a finding at the world muscle conference. This is what the genetic diagnosis would look like, for people who haven't seen one.

It is just a matter-of-fact mutation. What we did to celebrate the hard work of the people at the University of Sydney is, we had a celebration cake. We have the gene and the mutation on the cake, and this is with Angela, my wife, just celebrating. For me, finding the answer was the first step as the patient to actually fight the disease, and also know what was in store for me and my sister.

One of the reasons why it took awhile to find the mutation is this notion – I feel in my research, how

European-centric research is, a lot of what we know is based on European cohorts. What I'm trying to show is that the mutation I'm carrying is only found in East Asians and you can see that Europeans don't carry it.

And that's the reason why it wasn't prioritised in terms of the gene that was screened. What is obvious is my family from Cambodia were Chinese Cambodian, you can't apply what works for Europeans to people from every place of the world.

Onto the next story or journey and this is using sequencing, this was the emerging technology when I finish my PhD. It was amazing technology that allows us to sequence and find the letters of each gene in the whole genome simultaneously and rapidly.

No longer would we have to do it the old way. Before I talk about that I will go over the central dogma of genetics. We start with DNA, all the DNA content of each cell in the body is called the genome or the human genome. This is organised as chromosomes, we have 23 pairs of chromosomes for a total of 46 chromosomes.

RNA is sort of a copy of the gene. The instructions go out and we can make proteins from that RNA. That is the central dogma of genetics, something to keep in mind as I step through the next few slides.

The next-generation sequencing came in three flavours. The first is whole genome sequencing, and that is sequencing the whole DNA sequencing, the whole two sets of 3 billion letters, and it represents this apple.

We could achieve it in 2012 it was very expensive so we rarely did it. What was something that was more strategic and economic was to do exome sequencing. This is a 1.5% slice of that apple. This is where the genes are and also the coding bits of the genes.

The coding bits are the bits that have instructions to make proteins. This is the bit we actually understand the best. It is a very economical approach. Let's just seek with the bits we know best how to interpret rather than the whole genome, which is like the black matter of genetics, we are trying to understand what the rest of the genome does.

RNA sequencing takes this one step further. Perhaps we are interested in not only 20,000 genes also in the human genome, but only the genes that matter in a particular tissue. For muscle tissue we may be only interested on the mutations of genes in muscle. Another set of genes may not be expressed in muscle and may not have as much of an impact.

The old way, and this is the approach that was taken for my family, is that a patient would come into the clinic and get a clinical diagnosis. The clinical diagnosis would be based on the muscles affected, how weak you are, your family history. Based on that clinical diagnosis you go to a list of known disease genes and screen them one at a time, either the DNA or the protein, to see if there are any clues they were defective.

This is very laborious, one by one gene approach whereas the exome screening lets us examine them all at once, hypothesis free. This is what we did, the first family we sequenced in Boston for my project, and this was at the Broad Institute.

This was a collaboration with the University of Sydney, particularly Westmead Children's Hospital. A lot of the families that still didn't have an answer in terms of their genetic diagnosis. We called this

family A. You can see using the old approach of screening one gene at a time based on a clinical diagnosis, after nine years we still failed to find an answer for this family.

We wanted to see taking a new unbiased approach of sequencing all the genes simultaneously, would we be able to find an answer? One of the challenges is, if you have that much data from that many genes, how do you sift through it?

There are three main types of genetic variants you can get. One is synonymous variants and as the name implies, you don't change amino acid in a particular protein.

The next class are missense variants, the change changes the amino acid, changing one amino acid out of the whole protein. The last is protein truncating variants, and these changes either stop a protein from being produced or produce a truncated version.

We are most concerned with the last two because they are the ones most likely to have an impact on function and therefore cause disease. When we sequence our patient, we get just under 12,000 of those. Now we are most interested in which ones are common in the population and which ones are rare.

When you are looking at rare diseases, it's logical that it is the rare variance that will cause rare diseases because if it is a common variance, more people in the population would have that disease.

To make sense of that one exome that we sequence for the patient we have to ask the question in the context of tens of thousands of exomes, which are rare and likely to cause disease.

This is the project I worked on in Boston and this had never been done before, to create this large catalogue, firstly from 92,000 exomes and we subsetting it down to just over 60,000 individuals. There are several reasons why – one, we only wanted to keep the high quality exomes.

We had to filter out related individuals because related individuals share the rare variants and inflate that count. The reason we had to remove a lot of the 92,000 is not all the samples consented for sharing in this manner so we had to respect the consent and remove them before it we shared.

The last point is we had to get rid of people who had severe paediatric onset diseases because we were going to use this to interpret rare disease patients. One thing you may have noticed in the list of cohorts is there are a lot of common diseases like type II diabetes, but the reality is when you have a cohort of people in their 40s, 50s and 60s, you will get people with type II diabetes and heart disease.

What I would normally save this cohort is they are cohort of relatively healthy people. What this allowed us to do, for the first time, create a resource of unprecedented size and diversity. Colouring the different regions, people were using the ESP dataset to interpret their exome sequencing project, you can see it is quite large but in terms of diversity it only represents European Americans and African Americans whereas the resource we created has a much wider set of diversity, such as East Asians and also South Asians, which ironically make up a lot of the world's population.

There is still a long way to go in terms of increasing that diversity because the East Asians and South Asians, only one city or one part of those regions. We can increase diversity, especially in the non-European populations. But what people who use this resource do is filter out variation in patients' exomes.

We get somewhere between 600-1000 variants to under 200 rare variants found in disease patients and from that we can then decide which ones are likely to cause disease.

Going back to this problem, we can then go from just under 12,000, to 132 variants likely to cause disease. And using inheritance patterns, knowing it is a recessive disease, if you have two affected girls and unaffected parents, we could narrow it down to just one gene. The reason it wasn't discovered with the old method is this was a novel gene.

One of the gold standard is when you make a discovery is to show there are unrelated families with that same disease, that's a mutation, and also to create an animal model and show when you mutate the animal model for this gene, that has a similar disease.

It was a very satisfying thing to go from not having an answer for this family for over nine years and using this new technology available in the US to get this down to a few weeks from receiving the DNA and getting an answer for this family.

Ironically, the paperwork to get samples to the US took longer than the science itself. With this part, it was a major team effort in terms of the project to create that resource so the world could use it to filter and interpret genes and also working on the neuromuscular disease cohorts I worked on in Boston.

It is a massive team effort and one of the major collaborations was with the University of Sydney and Westmead Children's Hospital. And we collaborated around the world and locally in Boston, Massachusetts General Hospital and the Broad Institute, where that work was done.

In terms of the exome aggregation project, this was a massive effort of goodwill from principal investigators contributing their data to make up those 60,000 individuals. A lot of this data hadn't been published and the dataset, we made that available prior to publication because for us it was about trying to make the resource available, it not being on our timetable, but something we can make available as soon as possible and iterate on trying to make it a high-quality data set for the world to work on.

I will transition to the last story and this is showing some of the promises of personalised medicine. Something to show hope for the patients. One of the things I did have the good fortune of working on was getting to genetic diagnosis much quicker for rare disease patients, but if you are cynical you would say I am getting better at delivering bad news faster and I didn't want my career to be just that, I wanted it to translate.

What can we do knowing the exact knowledge of the genetic mutation, to actually help the patients? One thing I will touch upon before I go into that story is that during my years at the Broad Institute, one of the emerging technologies was CRISPR. When I left for the United States in 2012, no-one had heard of this, because it didn't become mainstream until 2014.

There are two components of this technology and it is a system from bacteria and it fighting pathogens for bacteria. Two parts of the system, the first is the guide RNA. You can think of the guide RNA is sort of like the address. Where in the human genome do you want to go to to bring a particular protein?

This protein, Cas9, has a particular function and that is to create a double break at this address in the human genome. When it creates that breaking DNA, what happens is the DNA repair machinery

quickly tries to fix it, and shoves any DNA there.

It's a great technology to precisely go to a part of the genome and disrupt the gene. But other researchers were working on ways to precisely edit, not just going to a particular place in the genome and disrupting it. That was the first application, how can we use it to disrupt and turn off genes and see what the impact was.

My collaborators at the University of Massachusetts said, "I think we have a way of fixing your mutation and we want to try it out." The first thing they wanted was a sample from me. I went to the University of Massachusetts and gave a sample, a skin biopsy, which doesn't hurt as much as a muscle biopsy, which I was thankful for.

This is the skin punch. The little punch comes in under a general and takes a little bit of skin. And from this, you can then convert it into muscle cells. The green is showing a muscle protein and the blue as the nuclei of the cells. So you can create muscle cells from it.

What they showed a month ago, which was the best 40th birthday present I've ever received, is a way of correcting it. This was published in the prestigious journal Nature. They were able to get just under 80% correction of the cells. So either both copies or one copy. But either way it was enough. They are trying it on an animal model, a mouse model, and I'm helping other patients around the world.

It is exciting to see it going from a genetic diagnosis to a way of correcting.

Inspired by this, starting up my own lab in Yale University, this is how the lab looked on day one in 2018. Very empty in the background, of Angela and I. This is how it looks in 2019. So the lab has grown quite big during that time, in that little year.

I'm going to end with a story of us working on personalised therapy. This is a patient with a DMD mutation and a form of muscular dystrophy. He is confined to a wheelchair, around 25 years of age. The mutation he has is the 30KB deletion, or 30,000 bases deleted in his DMD area on the chromosome.

I will try my best to explain this. This removes the first exon, or the first instructions to make the dystrophin protein, and you can see the absence of data right here that correlates to the deletion.

We were thinking that this deletion removes this region and stops us making the muscle for of this gene. But there are two forms. The non-muscle forms that are relatively intact.

So the idea is, why don't we tell the machinery to actually turn on these genes? This is borrowing off the CRISPR idea and using the Cas9 protein. Instead of telling the protein to go to a particular place in the human gene and create a double-stranded break, scientists have gotten clever and said, we don't want you to wreak havoc on the human genome and create double-stranded breaks. We're going to remove that ability to create it and actually tag on proteins that we want you to bring to a particular place in the human gene.

In this case, we are bringing in machinery to turn on genes. So now we can turn on genes that will replace the muscle and have very similar function. Because it is only the start of that gene that is similar between the two isoforms.

What we showed as a proof of concept in a cell that doesn't produce muscle proteins. First of all, on

the RNA level – if you remember, the central dogma of genetics, going from RNA to protein – we could show first of all using the control, we could show up regulation of another muscle protein, titin. This is probably 40,000 times what we would normally see in the cell.

And also switch on the muscle, and also the non-muscle isoforms as a way of showing we can turn other forms on that this patient can't actually express, to hopefully rescue this muscle disease.

We also have shown this on the protein level.

This is very preliminary, so for the scientists in the audience, this has to be repeated many times to make a better result, but I just had to show you the raw results of science before it gets cleaned up and repeated many times for a robust result.

What we are most interested in is not the expression of the RNA but the expression of the protein, because that is the machinery or the thing that is going to perform the function.

Here we can actually switch on the non-muscle isoforms in that patient. So it is one step closer to developing patient therapy. This is a genetic mutation in the patient wear, say, 10 years ago we would say, "That's it, that is your genetic mutation." Now we can say, "This is your genetic mutation, what can we do to address this?"

A lot of this has to be personalised. Previously we were limited to taking a one size fits all approach, like steroids is good for muscle wasting. Hopefully this will work for all patients. So now we can address the genetic root cause of the disease and not just the clinical symptoms.

With that, I will end. For this piece of work, it was a massive team effort from the team at Yale, particularly Keryn Woodman, and also Angela, who designed and performed a lot of the experiments to show the proof of concept.

There is a long way to go, but it is showing how we can use the latest technologies in genetic editing to achieve some of this personalised approach.

The last person I would like to thank is my wife, Angela, who has gone on every step of this journey with me, from the first story, the second and the third. For the 'Lord of the Rings' fans, sometimes I call her my Samwise Gamgee, because I don't think I would have gotten far without her on that part of my journey.

(Applause)

SANDRA COOPER:

It is quite an inspirational story.

I'm going to start the conversation tonight and speak with Monkol about a few things, with some notes I jotted down. But please put your thinking caps on, because I am going to reach out to the audience, and it would be wonderful to take some questions from the audience after we have had a chance.

Monkol, I think you have a really interesting background, coming from Cambodia to Seven Hills, University of Sydney, Harvard, Yale, and back to Sydney for the TED talk.

You are one of seven kids, only one of three of your year from Blacktown Boys High to go to

university. So what do you think it is about? You, your family and your background, that made you one of those three? And have you always been a terribly nerdy overachiever?

MONKOL LEK:

(Laughs) First of all, I would like to say that a lot of it is luck. Being in the right place at the right time, but also creating your own luck.

Two things have driven me. One is, not growing up with much and also seeing the sacrifices my parents made, and also my older siblings, so that I could have a good education and just concentrate on my education and not anything else was actually a huge advantage for me.

So I felt it was necessary to have that pay that self-sacrifice back. The second is, comparing the two the second or third youngest, I have always wanted to know how things work. And I think what frustrates me the most is when something is broken.

I'm the kind of person who, if something is broken, I can't sleep at night, I am always googling, trying to find out why something broke. So my body broke. And I think it is more important than a toy or remote control being broken. I really wanted to know why, type thing. A lot of it is luck, also.

SANDRA COOPER:

Sure. So your first training was in engineering and you got a job at IBM in computing. Was there a specific moment in time where you thought, "I'm going to go back and retrain to do medical research"? Was it one specific event or a combination of events?

MONKOL LEK:

I think it is a combination of events. Hopefully nobody in IBM is in the audience, but I had a lot of free time in that job. I had a lot of time to ponder and think about biology and genetics and things like that.

And I thought, I really need a good foundation because I don't quite understand everything that contributed. And a news article I found about research that was happening in Melbourne on muscular dystrophy.

I cut out that little piece of newspaper and I stared at that for quite a while. So there was part of me, it made me think a lot. Because part of me says that I can come here, work at IBM, be good at my job, work hard and sort of like get paid a higher and higher salary. But I will go home and be dissatisfied. Dissatisfied that I'm not using some of my skills and talents to actually help people with my disease.

So part of me thinks that... I like my neurologist and things like that, but it is kind of selfish for me to think that my neurologist would think about my disease night and day, would think about it in the shower, and on the weekend.

For patients out in the audience, no-one is going to care about your disease more than you, because it is actually affecting you. Especially if it is affecting you 24/7. So it is a combination of all of those thoughts, and major saying, "Let's just go on an adventure and see what happens."

SANDRA COOPER:

I can distinctly remember when you and Angela came to the lab, I think it was in either 2007 or 2008, and we met with Catherine North in her office. And I remember thinking, a husband and wife team, I'm not sure how this will go.

Sometimes I think it is difficult when your students are really close to the disorder they are studying, it brings great strength, but it also brings risk. And science is plagued by failure. You know, we learn from failure. We are experts at failing. We are very expert at failing.

And so you were there with Angela. And I guess part of the story is, you are not the only talented researcher in your family. How did you meet Angela, and what are the dynamics of working as a successful husband-and-wife duo?

MONKOL LEK:

I met Angela over the internet. This is before internet dating became a thing. This is showing my age – this was over a program called IRC. It was a chat program, a very basic text chat program. That is where I met Angela. Then Angela and I decided to do a degree, and what we were most interested in was biology and genetics, which gave us a great foundation.

I forgot the second part, about the husband and wife team? It has worked well so far. Mainly because I've worked on aspects that I am passionate about, and that is using data analysis of the big data that a lot of genetics actually produces.

Next Generation sequencing is just a problem at big data, how we actually sift through that to get the most informative pieces of information to answer a question. Whereas Angela was more interested in working on wet lab experiments. The experimental components.

So we have had our separate strengths, and then we can help each other on our strengths. But now we are sort of merging on some of the things we are both interested in, and that is translational things. It will be interesting how that goes, too, because we both have different opinions on how to achieve things.

SANDRA COOPER:

That's part of the magic, isn't it?

About Kids Neuroscience Centre – you know part of what drives us, the lifeblood of Kids Neuroscience Centre is finding genetic answers for families with rare disorders. It is incredibly meaningful for us. I wanted to show these slides.

Before next-generation sequencing, it would take two or three years to find the answer for a family. Did it take about two years to find yours?

MONKOL LEK:

No, much longer.

SANDRA COOPER:

Now we can do it in a week. It means so much to us, we celebrate every time. We keep going back to our unsolved families, we pull out families from 20 years ago without an answer, and every time there is a new technology, we go back and throw the kitchen sink at them.

We make cakes, hand decorated. And having you and Angela on our team was so meaningful, this was a quilt my teammate. I was Angela's supervisor and a little piece of decoration, all of our families made something and Francis sewed it into a quilt.

You won't see it without a keen eye, but in there is Monkol's genetic code. What did it mean for you

to find the specific genetic answer?

MONKOL LEK:

It was the end of one of the journeys of curiosity. Because knowing the gene that causes your disease gives you a lot of information, particularly if it is a known disease gene. You can know if there are particular parts of your body or symptoms you will develop and be very proactive about it.

For mine there will be a heart complication so I can be proactive about that and monitor the condition. It's much better to prevent rather than treat the symptoms later, if I haven't taken good care of myself. It's a picture or portal into the future.

Although my sister is older and has the disease, she is another portal into the future. It is the end of one journey, and also a way, as I showed in my presentation, now I know the gene mutation, I can approach other researchers and ask them if they are working on something that may help.

I was very fortunate that my collaborators at the University of Massachusetts said they could give it a try.

SANDRA COOPER:

How does it feel being on the other side? Scientists in the room will know the power that ExAC has brought to families with rare diseases. It has transformed the world, what Monkol and Daniel have built at the Broad Institute have transformed medicine.

Can you understand what it is like being on the given end of diagnoses? Do you find it meaningful yourself to know you've made such a difference for other families walking behind you?

MONKOL LEK:

I find it very satisfying because I know what it feels like. It is satisfying two ways, one, as a nerdy scientist, to know you've solved that problem. And second, it is great to deliver – I won't be pessimistic in saying this – good news for them because that is one stage of their journey. They can plan for the next stage.

A diagnosis can mean many things for patients. I will touch upon that. One, it can mean better lifestyle choices, like for myself. It could mean that in a case of misdiagnosis, maybe there is treatment for their disease.

And also to be enrolled in clinical trials. Clinical trials are becoming more specific because the therapies are becoming more personalised to people's genes and mutations.

And the last thing is that, particularly when I look at the mutation and I am realising that some of the technologies can work on this particular gene mutation, it's the next step to rationalise personalised therapy for those patients.

SANDRA COOPER:

I've been lucky in the last three years with our collaboration with Yale and Harvard, finding a diagnosis has illuminated treatments that have taken five individuals, depending on their power wheelchairs, they can now drive a car, and with assistance, walk.

You touched on something in your presentation – I didn't know what Monkol will talk about when I prepared my questions – hope and acceptance. For some families with genetic disorders, the genetic diagnosis is incredibly empowering but it can also confirm their worst fears that they have an

untreatable condition.

For many families it is life limiting. Speaking from my own experience, getting a rare disorder in my 40s and overcoming it, I know it is a delicate balance between hope there is a treatment but not expectation of it, and an acceptance of what you have.

I wondered if you wanted to share with the audience how you manage the delicate balance between hope that a treatment will present itself and you can be part of the solution, and acceptance that you may not, but you may forge a path that will help others.

MONKOL LEK:

When I first got the genetic diagnosis, there wasn't much acceptance, mainly because my muscles hadn't got that bad. There was part of me that said maybe it is wrong and I will get better.

Mainly because I didn't have that background in genetics, I didn't realise how deterministic that was, that diagnosis, when you have a monogenetic disease. And also a disease where they are quite certain you will develop, they may not know when and how severe.

Part of me took a long time to accept it. Also, it's hard to know that some of the technologies I work on for people at my age, that maybe this therapy won't be for me or be for patients that are much younger than me.

And also, a lot of these therapies will only halt the progression of the disease. We are not 100% sure if it will reverse it, but based on what we know, it probably won't reverse it. I probably won't be able to run again. It is acceptance that a lot of these therapies that although it addresses the genetic root cause, it can't reverse it. It is just stopping the progression of the disease.

For me, it's still satisfying even if it helps someone else and not me, know that I can use that technology to help. There was never the intention to go on this journey just to help myself. I'm thinking about my sister and other people who go through the same struggles as me.

SANDRA COOPER:

That brings me to gene editing. We can sequence a genome in five hours, and the power of CRISPR Cas9 editing is incredible. The genetic editing of yourselves must've been a wild night, that must've been crazy. To explain to the audience, what does this mean for you and where will you take this forward from here?

MONKOL LEK:

For me it was mind blowing when I got my genetic diagnosis. I didn't think there was a technology that could achieve such a thing with such precision. Letting people know in the audience that this technology has only been available for the last 3-4 years, and it's revolutionised all the different questions we can ask of genetics.

Manipulate the genome and ask what is the consequence of that. We've never been able to do with such speed and precision. It is sort of like a game changer in terms of the range of discovery, we can do things that the genome wide level.

For me, the next steps would be my collaborators want to try it on a mouse model to say, yes, we can correct cells, but one of the other challenges is can we deliver this therapeutic to where it needs to go. Where it needs to go is in all the muscles of the body. How can we deliver it to their hearts, a specialised and important muscle.

And what is the delivery efficiency, what is the right dose and is it safe? One of the hardest things when using this technology is – is it safe in humans? The next thing, one of the realities, to go to clinical trials, someone has to get a payoff.

You have to have a lot of patients for a clinical trial. We need to find more people around the world with exactly my genetic mutation. Every time I go back to China to try to collaborate and ask neurologists there, they find more patients. We believe there are more in Southeast Asia, and there should be a lot of people living in the US and Australia because people migrate now.

SANDRA COOPER:

I am a female neuroscientist, so I am a rare breed. But so are Cambodian Australians at Yale. One of the things I love about science and innovation is generally we are an inclusive bunch, we loved difference because difference is what leads to innovation.

As a Cambodian Australian at Yale with a disability, what are your experiences with Diversity and inclusivity?

MONKOL LEK:

I have to be honest, it's been very challenging, because although my body is disabled, my mind is not disabled. Yes, I take a long time to walk from A to B, it doesn't mean my mind takes a long time to get from A to B also.

For example, going to conferences, people worry if they are going to forget what they are going to say. My biggest worry is how I am going to get onto the stage. There are constant struggles, as scientists we have to travel a lot and my body can't take the travel.

I worry if I can make the impact. There are a lot of new paths I have to achieve. One of the things I got across to The University of Sydney, I was fortunate to get that across, when handicapped people travel to conferences, it costs a lot more because they can't get on the shuttle bus to get to the venue and things like that, they need a taxi.

The University of Sydney, to their credit, acknowledgement and gave me extra money to travel. It's the same challenges I have now, to overcome and make people aware of some of the challenges I have in terms of that.

The Cambodian part, not so challenging, I would have to speak Cambodian to say I was truly Cambodian. I think of myself more as Australian.

SANDRA COOPER:

This leads me to my next question and I'm sure many in the audience will be feeling inspired and reflecting on how lucky we are to be so passionate about what we do. I wanted to reflect on you transitioning to be a principal investigator at one of the most prestigious universities, we know that tall that the constant pressure of performance takes. It's not all roses, we are often on fixed term contracts or have people on fixed term contracts or have fixed term funding.

I know looking around me that a physical or mental health issue exacerbates that. Having reached this position at one of the world's most prestigious universities, what keeps you awake at night?

MONKOL LEK:

I can narrow down three challenges we have a scientist. One is where will the funding come from?

The next is people, how to get the best out of the people in my team. And the third is scientific ideas.

I will touch on all three. Being a scientist, it's a lonely place, having to come up with all these ideas for projects and championing those ideas when your competitors and other scientists think your ideas are crap. It is to go through with that.

And when you have a truly novel idea, people are going to question whether it is correct. You have to have that perseverance and self-reliance. But at the same time, not be arrogant and actually taking that feedback, that your colleagues think your ideas are crap.

The other thing is people. Now I appreciate the hard work that you, Sandra, and Cathy, go through, trying to get this out, not everyone is on the same page. Everyone wants something different out of their scientific career and they are trying to meet in the middle. You want this out of your career, but we need to get this work done. It is trying to get the healthy balance.

Sometimes that gets me up at night because I was trained to be a scientist, not a manager of people. It is one thing that should go into scientific training, especially people who are going to lead teams.

In the last is funding. Funding is getting harder and harder because there are semi-brilliant scientist to finish their PhD each year. In the United States we have this challenge that there is no retirement age. So brilliant scientists want to work until the day they die because they love the science and this is their life. I can't criticise that, but it makes it challenging, especially for federal funding.

One of the advantages we have in the United States that because it is such a large population that there are alternative sources of funding, and we can diversify our funds, our funding sources, such as patient foundations who want to see the science succeed and are very supportive, especially of junior scientists. And the second is industry, who want to see this translate and become a product that people can use to benefit their lives.

SANDRA COOPER:

Before I pass it to the audience, I've got one question for any aspiring young or not so young people in the audience would like to pursue genomics. Knowing what you know now and having been at the cutting edge for five years, what do you think are the skill sets that the University of Sydney and we should be increasing capacity in right now to meet the genomic needs of the next five years?

MONKOL LEK:

Heavy investment in data science. Like, how do we address the problem of big data, different methods of analysing big data, and how do we learn from the big data. A lot of things they are investing in the in the US is artificial intelligence and different statistical ways of analysing that big data. That is a good way of preparing young scientists or not so young scientists, for the next step, if they want to get into genomics.

And the other thing is, just understanding the translation. Genomics is a way of answering a particular question, and knowing the question it answers and the meaning of that question. Not just the big data component of it, predicting the first comment.

The last is curiosity. And the ability to think big and ask the question, 'why not?'

SANDRA COOPER:

If we were to get you back here in 10 years' time for another ideas night, what would success look like, if you reflect back on this night in 10 years' time?

MONKOL LEK:

In 10 years' time I would want to talk about some of the genetic technologies I touched upon going to clinical trials and showing its impact on patients. Overcoming some of those regulatory hurdles, we have to overcome safety hurdles and making this effective. And talk about some of the research that possibly myself and my colleagues have gone and benefited patients. That would be truly amazing.

And also, you know, one of the things I didn't touch upon is the genetic diagnosis rate is about 50% rare disease patients. So how have we moved the needle to get that close and closer to 100%? How have we taken advantage of the emerging technologies to get an answer for everyone?

SANDRA COOPER:

Can we take some questions? Sorry, such blinding lights in my face. I can see you at the front in the second row.

QUESTION FROM FLOOR:

That was a wonderful presentation. Thank you very much. I just have two aspects to this whole research came to my mind. I am not a scientist, just a layperson attending this out of interest.

One is, as soon as we talk about editing genes, I often read about, "What kind of monsters are we going to create?" Are we going to create new diseases we haven't seen before? There are those doomsday scenarios that come up the moment we talk about editing genes.

The other aspect is, people often argue that knowledge about genes and the causes is best left alone, because the moment we know what genes create what kind of diseases, we will get into further levels of discrimination, in terms of insurance and people being allowed to do things. There are all kinds of ways that people can be discriminated against the moment we know their genetic make up, and the diseases that they carry with them.

A question I would also like to ask you is, based on your own specific clinical trials and so on that you went through, what sort of unintended consequences did you encounter? And what sort of controls were in place to make sure that you are not going to be creating a monster?

MONKOL LEK:

This is a great set of questions. I will try and remember all three parts of that question, and you can correct me if I haven't touched on all three parts.

The first part is, being able to edit the gene and and edit genes, that we possibly could create new diseases that probably didn't exist, and things like that.

One thing we have to keep in mind is, what kinds of cells in the body we're editing. Are we editing things that can be passed on to the next generation, or not? So yes, we could accidentally edit a gene that causes cancer and things like that. One of the biggest challenges in CRISPR is the off-target effect. Yes, the guide takes the protein to a particular address, but sometimes that looks like another address in the gene, or very similar.

Everyone has had the experience of getting their neighbour's mail, so that is an example of the off-target effect. Sometimes the effects can possibly be another gene. There are a lot of extra safety that we have to go through. And the technology still needs to improve to make sure that we don't

actually have unintended effects on that point.

The second point was regarding, say, insurance, life insurance, and knowing the interpretation of a particular genome and things like that. I'm not the best person to answer this question, but I will answer aspects of it. You have to tease apart two concepts. One is, the diseases I touched upon, most of these are caused by one gene, they are called monogenic. The mutations in these genes normally cause severe diseases. If you have this mutation, you are going to get this disease. We don't know how severe or at what age, but you are going to have them. That is one category.

Another category are complex diseases. A lot of genetic variants across the genome contributing to a certain trait behaviour. An example of that would be a regularly be height, which is a complex trait. And other things like that.

And then there are complex diseases like Multiple Sclerosis and things like that. It has a genetic contribution, but it is not from one genetic variant but a lot of genetic variants making that contribution.

Thinking about monogenic diseases such as Huntington's disease and things like that, knowing that would affect health insurance and life insurance. I hope that regulation and protection of patients moves just as fast as the genetic technology. It needs to move a lot faster than how long it takes many laws to come into effect. It has to move fast, because this technology is moving pretty fast. Mainly because of the way you can adapt it to do so many different things.

And the third point you made, and I've totally forgotten other third point...

SANDRA COOPER:
I think that was it...

MONKOL LEK:
There were a lot of things in place, but a lot of things will probably be restricted at first to patients and diseases where there is no treatment available, and that is quite severe. And not treating it will lead to something fatal.

SANDRA COOPER:
There is very strict governance. Every time we do genetic editing, there are very strict governance roles for every experiment we do on human cells, and particularly as PIs there are a lot of restrictions around autologous manipulation, so manipulating Monkol's own cells would not be permitted. It would probably be another lab that would do it.

There is incredible regulation around it in first world countries. I think it is an excellent question. I think it is a very dangerous time. Regulation needs to keep up. We can take another question. One in the front, and then one behind.

COMMENT FROM FLOOR:
I wanted to say thank you for the talk. I have just recently finished an undergrad degree at UNSW. I am a research assistant in motor neurone disease and more excited than normally to go into work tomorrow.

I just wanted to ask, given the social context in which science is performed, have the actions last year of the professor at the human genome editing conference affected your work with CRISPR?

SANDRA COOPER:

Do you want to be more specific?

QUESTION FROM FLOOR:

The CCR 5 Delta 32 deletion in the twin girls.

MONKOL LEK:

I can speak to that, and probably Sandra can jump in with it with any further comments.

It did emphasise to me the importance of regulation and the importance of asking the question of why you are doing something, not just because you can, because there is not a good reason to do something, because you can. Because you are dealing with human life here and the impact of it.

Like what Sandra said, to answer the third part of the question, is that there are a lot of regulations in first world countries. And it is not something that I can go out and do. It is something that I have to get approval, first of all from human ethics committee and also if it is going to go into clinical trials in the United States, from the FDA, that regulate a lot of those things.

We are in new territory and we are trying to understand the impact this will have and a lot of it will have to go through a lot of public debate, also. But that's what it made me think – that you can't do something just because you can, because it's the wrong reason to do something.

SANDRA COOPER:

I personally feel we are moving a bit closer to 'Gattaca' than I would like, for those of us of a certain age in the audience. I think there is a lot of agreement in the scientific community that genetic manipulation of somatic cells is acceptable in terms of treating and curing disorder, but genetic manipulation of the germ cells brings a different complexity, because you can pass on the genetic editing event to the next generation. And that brings up a hugely more complex area.

QUESTION FROM FLOOR:

As a non-science person, I've just got one question, but just to explain how I got to that point...

One of my sons was born with pulmonary stenosis, which is a problem with one of the valves of the heart. And the consultant says it is genetic. Then another son was diagnosed with scoliosis. And my father-in-law with Alzheimer's and my mother with multiple myeloma blood cancer.

In each case was really interested, because there were ramifications for whether they have children and their future health. So I said, "What will happen next? Will this be passed on to the next generation?" The doctors said they didn't know. My question is how are you getting to the consultants and down to the GP family doctor level with this information, both in terms of diagnosis, but also in terms of which things can be treated in different ways?

SANDRA COOPER:

Many of the disorders you speak of are not necessarily monogenic, where one gene is the primary cause of the disorder. I can't speak particularly about your particular constellation.

Everything essentially is genetic. The reason you look different or similar to the people next to you is genetic. When the doctor says it is genetic, certainly is, but whether the phenotype is due one single gene or a constellation, it is hard to know. If it is monogenic, you probably would have been screened but it is probably polygenic, a whole constellation of things happening, so they can't give you information about the next generation.

I think genomic medicine is happening so quickly and I know a lot of the consultants and specialists are struggling with the speed that it is happening. I can only imagine GPs are struggling because it's not their primary training and it's a hugely complicated area.

It's a great initiative. If you think that clinical whole exome sequencing only came in in 2015/16 and in Australia it's only been implemented in the last three years. It is happened at tertiary referral centres, it is not conducted from GPs' offices.

I can't speak to what is going on in the health system, all I know is it is coming on quickly and the infrastructure in the health has not come on as quickly as the demand for testing has. We have a gentleman here...

QUESTION FROM FLOOR:

Thanks for a wonderful talk and welcome back to Sydney. I'm incredibly grateful for the work you guys have done. My question is for both of you, you are both uniquely placed with a raft of clinical trials coming down for rare diseases to say – what does a patient see that makes them want to enrol in a clinical trial and what it would need to deliver?

SANDRA COOPER:

That's a tricky question.

MONKOL LEK:

Try to answer this as patient. To know that it's not generalised or personalised to say my gene or my mutation because I see that more likely to be beneficial rather than something general rather than a dietary supplement which people have tried in the past.

I know it's ironic to say that probably the more risky ones because it probably has a greater reward. Having said that, we are in new territory where some of the gene therapy, clinical trials, if you try it once, you only get one try at it in terms of the benefits it delivers, because your body has built immunity and you can't do it again.

That means the way we do placebos is different too because people know if it has a good chance of working, the challenges we have from my experience of seeing colleagues do clinical trials, is no-one wants to be the placebo anymore.

They don't want to see their child not hit the milestones and watch another child who wasn't on the placebo hit the developmental milestones. Having clinical trials with bigger impacts effects who wants to be a placebo and who doesn't, and how we design that.

For myself, I want to go for things that are more personalised to my condition, rather than a generalised one.

SANDRA COOPER:

Shall we take one more question?

QUESTION FROM FLOOR:

I was wondering to what degree the technology you are working on is, for want of a better term, open source? And if you were to discover something profound, meaningful, impactful to humanity, the degree of vulnerability that discovery may have from a government wanting to seize it for commercial benefit.

We are seeing in America some pharmaceutical products being priced astronomically. If you get a discovery, may it get taken away and you have to pay a huge fortune to access that?

MONKOL LEK:

I will talk first of all about the data. The Exome Aggregation Consortium project, that was to be shared with the world. They can use it to interpret genetic mutations in rare disease patients. It has created a new paradigm of datasharing, not just datasharing but data accessibility.

A lot of things before that in theory was datasharing, but the true spirit of datasharing is to go to a website, write what you want and get what you want. Rather than going to a website, filling out hundreds of forms and getting what you want six years from now.

Datasharing has to be coupled with data access. But what has advanced, some of the gene editing technology, is the open source aspect of it. There is a new revolution, if you develop these technologies, to make it available in a central depository.

The one that is used in the US and I think also Australia is called Addgene. You deposit toolkits you create there and that becomes a library you order from. All you pay for is the cost of shipping and handling. You are getting that technology free and all you have to do is acknowledge you used it in a publication or somewhere else.

I don't know what it means for patents afterwards and who gets what money but at least that has accelerated this CRISPR technology, the concept of putting your stuff on the library, people can get the toolkit shipped to them, you can make modifications to it, add to the library of knowledge, people can get this modified thing, and that has accelerated the idea of not just datasharing, but sharing the resources you have created to manipulate the human genome.

SANDRA COOPER:

The world of academia is pretty orderly. As long as you are a not-for-profit academic, you can use the reagent, you can't go on with a commercial product yourself. We tend to play nicely with one another. We have time for two more questions.

QUESTION FROM FLOOR:

Monkol, I have a question. You have been living with LGMD for quite a while. You were mentioning in your talk earlier that you had disbelief when you first were diagnosed. From then until now, you probably recall all the activities you've done and whether they might have accelerated or otherwise your rate of progression.

With that in mind, do you think genetic diagnosis of families should also be complemented with what their potential prognosis could be? And what activities they should restrict to avoid accelerated deterioration, especially in long-term physically degenerative disorders?

MONKOL LEK:

I think that is a fantastic question. Like I said, I was using my older sister as a portal into the future of what may or may not happen. It's a difficult question to answer, mainly because there is also an effect on the environment, lifestyle and things like that.

It's hard to do that in a controlled way, knowing what activities to avoid and things like that. But what we do know is that the thing a lot of the rare diseases, where there is a sizeable patient community or population, is natural history studies.

Instead of looking at family members, you can look at a whole cohort, they have checked in each year, the progression of their disease. It is a controlled way of asking that with the numbers, instead of having just one patient or that being your sibling.

Because they could have been many factors why they could have deteriorated faster. We know for a fact that different family members with the same disease progress at different rates, and we don't know how much of it is genetic, how much is lifestyle and environment.

It's an interesting question. There is the hope that natural history studies and studies similar to that can ask that question in a very controlled way of getting to that answer.

QUESTION FROM FLOOR:

I am interested in all this stuff, but I was wondering about what you are saying about monogenic disease. If they are not specifically monogenic, I know for autoimmune disease there is a genetic correlation established but they are not sure what it is, if it is not monogenic, if they found a specific gene but it wasn't the sole cause, to what extent is somatic gene therapy is applicable?

SANDRA COOPER:

I don't think I have an answer. It depends. There are strong associations, Apo E ones for heart disease. It's possible you could make a difference in apologetic disorder. That's more of a comment. That's a good question, I don't think there is an answer in science.

COMMENT FROM FLOOR:

We are affiliated to someone who is suffering from an autoimmune disease and we were wondering how much somatic gene therapy could help. I was wondering if there is an ethical boundary that should be drawn.

SANDRA COOPER:

One of the questioners tonight is a transplant surgeon and he is looking at rejection theories. We are faced with that conundrum of when and where should we genetically therapise someone.

MONKOL LEK:

To touch on the question of it being ethical to treat it, with the complex diseases, the monogenic diseases, a lot of my colleagues in the Broad Institute work on complex diseases such as autoimmune disease. A risk is associated with a set of genetic variants. A particular gene or variant confers that risk but because it is a risk associated with a particular disease and it is not deterministic, I don't think it's ethical to make modifications if it is only a risk, and if it is a small risk, you are thinking of risk/reward.

If it is unlikely you will progress and get that disease it would probably be unethical to do that as a prevention.

SANDRA COOPER:

I have to wrap it up. I would like to thank all of you to give up your Monday evenings to share with us tonight. It's been wonderful to have you all. I would like to thank Alana and Chevoy, our Auslan interpreters, they've done a great job.

(Applause)

My thanks also to The University of Sydney, for hosting us in this wonderful room, the acoustics are

amazing. They don't build rooms like this anymore. And I want to thank Monkol, I'd love him to come back to Australia one day. How could we entice you back?

MONKOL LEK:

(Laughs) That's a difficult question to answer. At the moment I really like some of the cutting edge technology in the US but I see a time where the innovation that happens in Australia will be on the same par. And I would love to come back to bring some of the experiences and technology, and sort of like the culture, the good parts, back to Australia and meld it into the great parts of Australian culture so we can be on the cutting edge of scientific and medical research in Australia.

I think the thing that will most likely bring me back is that Australia has a centralised healthcare system and, having that, you can achieve so many things in the world of genomics and genetics, having access to that rich amount of data in a country that is not too big and not too small, you can make that impact. I see all those benefits.

SANDRA COOPER:

I know there is a Cambodian word you know, what does Monkol mean?

MONKOL LEK:

It means happiness.

SANDRA COOPER:

Thank you.

(Applause)

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