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#389: Genetic find and replace with CRISPR: Technology that will revolutionize medicine and agriculture

VOICEOVER
This is Up Close, the research talk show from The University of Melbourne, Australia.

ANDI HORVATH
I'm Dr Andi Horvath, thanks for joining us. Today we bring you up close to the world of cutting edge gene manipulation technology and in particular, one called CRISPR. Whilst it sounds like a kitchen appliance for deep frying, it's actually a revolutionary precision tool for genetic engineering, useful in both disease research and therapy. Adding to the soup of acronyms, we need to include Cas9, which is a protein that, as we'll hear, has supercharged the power and utility of CRISPR.

Advances in genetic engineering up till now have allowed for the manipulation of genes, but translation from the lab to human gene therapy has proven elusive. Meanwhile, gene editing has been really slow to go from the lab to the clinic, but now we have the awkwardly named CRISPR, which stands for Clustered Regularly Interspaced Short Palindromic Repeats. CRISPR harnesses a natural process found in bacteria, which have for eons been doing their own splicing of foreign genes and DNA self-repair. It is, in fact, bacteria's way of dealing with virus attacks. If a bacterium survives a virus attack, it can better its chances in future attacks and it does this by tucking away a virus gene sequence into its own bacterial genome, amongst the palindromic sequences, like a photo ID catalogue of bad guys to avoid in the future. Next time the virus attacks, clusters of so-called Cas proteins associated with CRISPR pick up a photo ID RNA and slice the virus.

But as we'll hear, CRISPR-Cas9 applications go beyond that, including the potential to therapeutically swap out genes that trigger diseases. Its power has been well demonstrated in laboratories with agricultural and human trials now getting underway. But while technologies using CRISPR-Cas9 look to have a bright future, they bring with it a number of ethical and regulatory complexities.

Joining us to slice and dice the topic of CRISPR-Cas9 is Professor Jacob Corn, who is the scientific director and principal of the innovative Genomics Institute at UC

Berkeley, where he leads the Corn Lab in development of next generation genome editing technologies. Jacob is in Melbourne as a guest of the Walter and Eliza Hall Institute of Medical Research. Welcome to Up Close, Jacob.

JACOB CORN
Thanks very much.

ANDI HORVATH
Jacob, tell us about these Clustered Regularly Interspaced Short Palindromic Repeats. How can you describe it for those of us who aren't geneticists?

JACOB CORN
I think you did a great job of introducing the idea behind CRISPR and how bacteria use these systems. The whole idea is that bacteria needs some way to fight off viruses and what they do is they grab little pieces of invading viral genomes and stuff them into their own bacterial genomes and then use these Cas proteins to make little pieces of RNA off the viral DNA and re-recognise the invading virus. So you might be asking yourself, well what does this have to do with genetic engineering and the key understanding here is if these Cas proteins are using pieces of RNA to recognise some other foreign piece of DNA, that other piece of DNA can be anything. So the connection here is that you can engineer a genome by inducing a cut inside of it.

That seems kind of weird. How does making a cut let you engineer something? It's because of something called DNA repair. All organisms, whether yourself, trees, anything, has DNA repair enzymes and we have to have them because when you walk down the street on a beautiful sunny day like it is here, you get UV damage as your cells are copying themselves, they accumulate damage and if we didn't have ways to repair that damage, then we'd be in big, big trouble. In fact, that's one of the ways that cancer accumulates, is when we don't repair that damage. So our bodies contain a whole host of ways to repair damage and one of the types of damage they repair is cuts in genes.So the way genome editing works is you get a Cas protein to target a certain place and it induces a cut and then DNA repair takes care of it. How does that lead to editing? Well there are two ways that the repair can go on. The first one is you can get error-prone repair, so the cell tries to repair it and does a kind of bad job at it, adds in a little bit of sequence, takes out a little bit of sequence and that breaks whatever happens to be there. So if that cut is in a desert, in the middle of nowhere, nothing really happens. If it's in the middle of a functional sequence, then that sequence gets broken. So that's really useful from a research point of view, because very often during research the way we figure out what cells do, the way they work, is a little bit like taking a car engine apart. You have a car engine, you want to know how that car engine works, you take out a piece, a single piece and you say, okay, what happened. You've got the catalytic converter, you take the catalytic converter out and you say, this engine now doesn't work, why doesn't that work, what does a catalytic converter do in that engine? Same thing with cells; they've got millions and millions of pieces, you break one piece and then say, okay, the cell no longer works, why does it no longer work, what did that part do, because we don't know what all the parts are. But where do you get to therapy from this? Obviously it's

very hard to make therapies that have to do with breaking genes all over the place, that's tough. So the other way that cells can repair DNA damage uses things called templates of other pieces of DNA. Normally during DNA repair a cell will use its own bits of DNA to repair the damage, so you've got multiple copies of chromosomes, maybe one of them gets broken and then you repair off the one that didn't get broken. But as researchers and clinicians, we can add in our own pieces of DNA that we want to put in and that can be useful because let's say someone has a genetic disease and the genetic disease is a single, small point mutation, one base out of the billions of bases is wrong. If we put in a template that contains the base that does not contain that mutation, the cell can use that, copy off of it and now the cell no longer has the disease causing mutation.

ANDI HORVATH
Right, so it's sort of like a car that can repair itself, but except what happens is the Cas9 protein is kind of like the mechanic that goes in and says, hey, that bit's not working and then other proteins say, well we're going to fix that because the Cas9 has just removed the broken bit. But what we're doing as scientists is that we're giving those other proteins, hey, put in this bit into the car because it'll work better with this particular broken bit.

JACOB CORN
Exactly right. I mean I might even say that the cell is sort of a team of technicians. Think about when you're watching Formula 1 and all of those technicians are coming in to help repair that car. Cas9 is the thing that sees the broken thing and points out to all those cellular technicians this is the thing you need to fix and here's the way you need to do it and then the cell is responsible for taking care of it. That's the big challenge actually, because if you think about all those technicians, we don't actually totally understand all the ways that cells repair DNA. So one of the challenges for genome editing right now is it works in many cases, but there are other cases where it doesn't work and we don?t actually know why. So better understanding of the way cells repair DNA will help us make this a more reproducible, more efficacious process for curing diseases.

ANDI HORVATH
Sure. So we can actually give those other proteins, say, hey insert this good DNA instead of that bad bit. So tell us the difference then between gene editing and what CRISPR technology actually sounds like, which is kind of like a gene therapy, because you're replacing the bad with the good.

JACOB CORN
Yeah, so there is really a place for gene editing in gene therapy. Gene therapy is where you take a virus and it contains a gene payload and you deliver that to a patient and that gene is now integrated into their genome but it does so randomly. That's useful because let's say that you have someone with severe combined immunodeficiency, it's also known as bubble boy disease, you've probably seen movies and heard about patients like this, they're lacking an immune system. They're lacking an immune system because they're lacking a functional version of the

protein. What gene therapy does is it introduces a functional copy of that protein, but it does so randomly and so there can sometimes be problems because what if you add in the good gene but it goes into a bad place? Gene editing can actually help gene therapy because now instead of putting the good gene randomly and sometimes goes in a bad place, you know exactly where it's going to go every single time. So gene editing actually helps complement gene therapy, but it also adds this new capability of being able to not only put in whole big things like genes, you can actually change little point mutations. That's really important because a lot of the human mutations that cause disease are not big, huge things that break a lot of stuff, they're little tiny problems. Let's say you have a broken gene, but it's broken in one little place. Rather than try to take the whole big thing and put it randomly, let's just change the one little bit that's broken and leave everything else alone.

ANDI HORVATH
Okay Jacob, let's talk about the case study of sickle cell anaemia. How has CRISPR demonstrated its power in that particular condition?

JACOB CORN
So sickle cell anaemia is a really interesting and in some ways a very medically frustrating case. So sickle cell anaemia is a genetic disease and it's caused by a single mutation. The frustrating thing is we've known the cause of this mutation since 1949, is when it was first described. We've known not only how it's caused, we've known even the mutation since 1949 and yet most of the way that we treat this disease is by giving patients painkillers because it's a genetic disease; there's no cure for genetic diseases. So the promise of gene editing is the ability to actually go into the genome itself and rather than try to address symptoms, e.g. with painkillers and things like that, to treat the disease.

Now gene editing itself is actually not a new concept. Gene editing has been around since the '90s using other types of tools. People have tried to do gene editing for sickle cell using other tools, they've had some success but the efficacy has been somewhat limited. So the hope would be that gene editing using CRISPR could maybe have some sort of benefit. So my lab as well as a couple of other labs have now been trying to use CRISPR to go after sickle cell disease and to do that, you have to go after these certain types of cells in your bone marrow called hematopoietic stem cells. It's really important because sickle cell disease is a disease of the red blood cells, causes them to curve up, causes them to clog in capillaries. But red blood cells have no nuclei; they have no DNA in them. You can't edit them, there's nothing to edit. So what you have to do is you have to go all the way back to the stem cells that make the red blood cells. So you edit those hematopoietic stem cells in the bone marrow, that should then give some sort of lasting benefit. So what we and a couple of other labs have shown is that CRISPR can be used to take the certain point mutation that causes sickle cell disease and change it back.

ANDI HORVATH
Now are you talking about cells in a petri dish, or are you talking about injecting a

whole animal, like a mouse? Also, whilst you're saying you're editing the genes of the hematopoietic stem cells, how many of those are going to actually make an impact and isn't there also a cluster of hematopoietic stem cells that haven't been edited? So is it a numbers game? How does it actually work?

JACOB CORN
That's actually a really deep question. So first off, you're asking a difference between two things that we scientists call ex vivo editing and in vivo editing. Ex vivo editing means you take bone marrow stem cells out of someone, edit them ex vivo, that is out of the body, and then put them back in. So that's where we're going right now and the reason that's very attractive is that it's basically just a bone marrow transplant, but you're letting patients be their own bone marrow donors. Instead of taking bone marrow from someone else that's healthy and putting it into someone with the disease, you take the patient's own bone marrow, take it out, edit it so that it now no longer has the disease and then put it back in.

ANDI HORVATH
So you're taking out all the bone marrow, essentially.

JACOB CORN
You take out as much as you can, you try to expand it.

ANDI HORVATH
Wow.

JACOB CORN
Yeah.

ANDI HORVATH
Have we actually done this with mice or with humans yet?

JACOB CORN
Sadly we've not done it with humans. We have done ex vivo editing using tissue from people with sickle cell disease, we've put it into mice, we've not done so at these huge scales. So that's actually something that we're working towards right now. One of the things we're working towards right now is taking some of the initial successes that we've seen in the lab, which are exciting but still relatively small scale and try to expand them to full clinical scale, billions and billions of cells and very importantly, we need to do so under conditions that are appropriate for safety and quality recording that you might use in a clinical trial. So some of the work that's going on right now is really just trying to take the things we've already done in the lab and do it again, but in sort of big-league mode to practice before we start trying to enrol people in clinical trials.

ANDI HORVATH
So these clinical trials are going to happen soon as we speak, in 2017?

JACOB CORN
It's hard to say exactly when they're going to start because a lot of it will be driven by the data. We're very optimistic that within the next couple of years we would be able to get to a clinical trial. I think there are a couple of groups that have said, we want to be in patients by X date. My philosophy personally is to say, well, we need to do the work, we don?t know what the result is going to be, so let's do the experiment, let's try to do the scale up, let's see how it goes. Optimistically, I would like to say yes, we could be there in a couple of years, but we have to see how the work goes.

ANDI HORVATH
If you are your own donor, that means you no longer need transplants from other human beings and there won't be problems of rejection. But, as you say, there are still questions of safety to iron out.

JACOB CORN
Yeah, so not rejecting the graft is one of the big benefits. There are a couple of problems with getting a bone marrow transplant from someone else. Number one, graft versus host disease means the thing that you get fights your body and then of course you yourself see the graft as foreign. So people go on immunosuppressants, etcetera, etcetera, it's a complicated procedure. So our hope is that doing this type of ex vivo editing will get around some of those things and make them safer. But we do need to make sure that the act of editing the bone marrow stem cells doesn't cause problems itself. So there are going to be clear safety benefits that editing will help get us around, but we need to make sure that we're not introducing new safety problems at the same time.

ANDI HORVATH
Sickle cell anaemia is part of a class of ailments that are caused by a single gene, but what about multi-gene disorders and other syndromes where the disease is due to a number of genes, does CRISPR have capacity there?

JACOB CORN
I think that the jury is still out on that. In the culture dish, people have been able to edit multiple genes simultaneously and one group has even managed to edit multiple, many, many, many locations in pigs, so things have looked okay, but obviously editing in pigs where if something goes wrong, you can just breed that out and breed healthy pigs against edited pigs, or just look for more pigs that are healthy, that's a luxury you don?t necessarily have when you're working with patients. So I think there's a lot of promise for working with multi-gene disorders and certainly CRISPR is nice because it gives you the flexibility to reprogram very quickly and look at a lot of different things. I think there's promise there, but a lot of that promise is really in the lab and on paper and I think the next couple of years are going to be really exciting because we'll find out can you actually go for multi-gene disorders.

ANDI HORVATH
I'm Andi Horvath and you're listening to Up Close. In this episode, we're talking about

the revolutionary gene editing technology known as CRISPR-Cas9 with molecular biologist, Jacob Corn.

Now I believe scientists are also excited about using CRISPR-Cas9 - can we just call it CRISPR - as a cell model for disease. Tell us about that.

JACOB CORN
I'm really, really excited about the promise of CRISPR-Cas9 - CRISPR - for treating genetic disease. But I think that really some of the biggest effects that are going to come out of this are actually the use to model disease and to do basic research. This is where we get into sort of unanticipated, new realms of discovery. CRISPR itself, it's a completely fundamental curiosity driven thing. CRISPR is this weird antiviral immune system. No one was looking for a gene editing tool when they found CRISPR systems and yet it turns out that this thing, discovered purely by scientific curiosity, actually is going to have a huge impact on human health. So imagine what's going to imagine now when people take this new tool and they start asking new scientific questions that they just couldn't ask before. I think there's going to be a huge amount that's going to come from this.

Last time I looked, there were thousands of papers that were starting to use CRISPR, most of them are not looking for genetic disease, they're using it as a tool to say, how does this system, work, how does that system work. As an example, maybe someone uses CRISPR to look at some little crustacean, maybe like some weird little crab that lives in the ocean. You might say, oh what's the point of that? But what if this crab actually can regenerate its limbs really well and we have no idea how that happens and using CRISPR lets us understand that better. Doing that gives us ways to perhaps look at better ways to heal wounds, maybe to help veterans coming back from combat situations to heal wounds and to repair damage from that. These are totally unanticipated discoveries that could have new benefit for human health. I think it's really important that we're able to use these new tools to ask these kinds of questions.

ANDI HORVATH
Wow, this would also have insights into areas like cancer and oncology.

JACOB CORN
Absolutely, I mean I think that goes multiple ways. Of course you can use CRISPR to ask how does cancer cause all these cells to start dividing too quickly, but remember, CRISPR itself is a process of DNA repair: you're cutting genes, you're inducing DNA repair. One of the hallmarks of cancer is problems in DNA repair because cells go crazy, they don?t repair their genomes, problems accumulate and so not only can we use CRISPR to ask questions about how do cells go wrong during cancer, the very act of doing CRISPR is fundamentally giving us insight into one of the primary mechanisms by which cells become cancerous.

ANDI HORVATH
Jacob let's go in another direction. CRISPR-Cas9 has broader applications than just

human health. Tell us about how these have been used in mosquito populations to help control the spread of malaria.

JACOB CORN
So what you're describing is a technology called gene drives and I really want to stress a gene drive is not something that is being used in the wild just yet, in fact when people are using gene drives, they're doing so in very, very safe, high quote-unquote biosafety level containment. They're not doing this because there's any sort of disease associated with it, they're doing it because they want to be very, very conservative and make sure nothing happens. So what a gene drive is, is a way of taking a trait and making it spread through a population very, very quickly. So what might this be useful for? In mosquitoes, they get infected by the parasite that causes malaria and one of the problems is, well how do we combat malaria? We can combat it in people but one way we could combat it is by trying to keep the mosquitoes from passing along malaria. So what if you could make a trait that prevented mosquitoes from getting malaria in the first place and then spread that through the mosquito population. It would be very powerful, there would still be mosquitoes around, bats would still have something to eat, it wouldn?t be a problem, but the mosquitoes just wouldn't carry the parasite anymore.

So it's an exciting technology, but people are being conservative because of course we're talking about taking traits and introducing them not in the lab, not in the patient, but spreading them entirely throughout a wild population, so people are get a little worried about it. Now I want to point out that actually gene drives are natural things. There's this weird thing called a P element that right around the '50s spread through all fruit flies in the entire world, completely spread through, it's a natural gene drive. So gene drives happen in nature, they're not this totally human synthetic thing, but when we start talking about making our own gene drives as people, we want to be very careful about how we design them and how we put them together. So there's actually a lot of both experimental work as well as just purely theoretical population genetics work trying to understand how they spread, how we can control them, as well as once we put them in, people have started to devise ways to turn them back off again.

ANDI HORVATH
Are there other things beyond insects in which CRISPR can be used for?

JACOB CORN
Well it's interesting because New Zealand has recently suggested that they might use gene drive technologies to try to take control of rodent populations that are out of control.

ANDI HORVATH
Sure, which are introduced animals.

JACOB CORN
Exactly, so invasive species, so it is possible that gene drives could be used to

control other invasive species. I think that's an area where we have to be a little cautious because there's a long history of trying to control invasive populations by introducing manmade other populations and sometimes those have gone okay and sometimes they've really backfired. So I think that it's a really interesting idea and I think it's probably better than, say, spraying poison everywhere that will then enter into the food chain. But we do need to be careful about introducing a genetic tool that could spread through a population to control another one, but it's one of those things that we need to try first in a controlled environment before we put it into the wild.

ANDI HORVATH
I can see CRISPR technology is also going to be helpful for broader global issues like food security or even the realm of biofuels. What's going on in that field?

JACOB CORN
I think there are a couple of really important things happening in CRISPR for agriculture. Using CRISPR in plants and animals I think is going to be a huge area for the world. As an example, back at my home in California, there's someone trying to use CRISPR to figure out how a plant called cassava gets attacked by a virus. Now cassava is a major food source for 80 per cent of Africa, it's a huge, huge source of calories for most of the continent and yet it's really susceptible to a certain type of virus called the brown streak virus. People really don?t know how does this virus get spread, is it possible to combat it and instead of combating the virus, which of course is going to be constantly evolving and trying to get away from anything you do, people have talked about instead what if we can make cassava that's resistant to the virus and then we can just grow that cassava. The virus is still going to be out there, but we'll be able to have cultivated types of cassava. It's one example in which there's a lot of food security benefit there.

There is even benefits just for stuff that might make your life nicer at the dinner table. Someone has recently shown that you can take mushrooms and keep them from turning brown all the time, just by making a simple change with CRISPR. The use of CRISPR in agriculture ranges everything from totally critical security, keeping food sources around, to just making the products that are on your dinner table more appealing, taste better, last longer. But one thing to remember about using CRISPR in agriculture is that what we're talking about here is actually not something really new, plant breeders do this all the time. When you take two plants and breed them together to make a better tomato or a tastier piece of corn, what you're really doing is you're swapping genetic information.

So when people are using gene editing in agricultural species, they're doing the exact same thing the plant breeders would do, they're just doing it faster and in fact they're doing it less randomly. Usually what people do when they breed is they take two plants, they put them together, bunches and bunches of stuff happens and it takes years to sort out everything that happened. What we're hoping with CRISPR is we can say, look, we want this plant to do X, we need it to grow faster so that farmers can get more yield, we want it to be more frost resistant, for example. We know how to do that and let's just implement that as opposed to breed two things

together and then spend the next years trying to sort out all those random junk that happened.

ANDI HORVATH
Concerning agriculture, genetically modified organisms have caused huge societal concerns. How will using CRISPR be different, if at all?

JACOB CORN
I think when people think about genetically modified organisms they're very often thinking about cases in which people take a gene from one place, totally different place and they put it into another organism. But it turns out that's not the way you have to do things and in fact, when you take two plants and you breed them together, what you're typically doing is you take one plant that has some random differences in itself and another plant that has some random differences in itself, they have some traits you like and you put them together. There's a way with CRISPR to rather take some gene from some totally other organism, but instead to just put in the little change that you think would be good. So instead of trying to breed these two plants together, you instead just get what you wanted out of it in the first place.

ANDI HORVATH
Right, so it's not a hybrid.

JACOB CORN
Exactly, it's not a hybrid, you're not introducing foreign genetic material. The mushroom browning is a great example. There's a mushroom that has been made that does not brown and what they do is they take an enzyme that's made by the mushroom that causes it to brown and go bad. All they do is they just turn off that gene. They're not introducing something foreign, they're just doing something that over time the mushroom will accumulate genetic errors and you might get that browning randomly by chance, but instead of waiting for a million years for it to happen, you just do it right then.

I think that right now there's a really big discussion among a lot of different countries about what is going to constitute GMO and what is not going to constitute GMO. So in Europe and in the United States, they have decided that making these types of small changes like you do with the mushroom are not regulated as GMO because they're changes that could happen naturally, we're just going to do them ourselves. But what will stay GMO is, say, taking a gene from a bacterium and putting it into a plant, that will stay GMO. But things that would just happen randomly that instead we're doing with CRISPR, will not be regulated as GMO. Other countries have decided that that's not going to be the case and using CRISPR will be GMO. Now I think there's a danger to the latter. This is the so-called process versus product debate. If you regulate the way you make the thing, then you're saying, well look the method you use to get there, however long it took, is what matters, not the final thing that ends up on the dinner table. I think a lot of the rest of the world is saying, look however you got there, whether it took you 20 steps or whether it took you one step, what matters is where you got to. Whether you got there by conventional breeding or

whether you got there by CRISPR, what matters is where you got.

I favour the product because I think there are all sorts of different ways of getting there. We may invent some brand new technology in five years of doing it in half a step that's even faster than CRISPR, who knows? If we start regulating the process, we're constantly playing catch up with technology and we're constantly trying to figure out what's going to happen down the pipe and what we need to think, I think, instead about is what are we comfortable with in terms of the agricultural product in the end. Since the things that are coming out the other side are completely indistinguishable from what you would get from normal breeding, which we've been doing for thousands and thousands of years, to me it makes sense that we regulate it the same way we regulate normally bred agricultural products.

ANDI HORVATH
Jacob what are the risks here? Is there the equivalent of the overuse of antibiotics that might lead to the creation of hardier pathogens and pests?

JACOB CORN
In terms of gene editing itself, it's pretty flexible, however there is one niche problem that might happen. So when you're making a gene edit, you're using a protein that's going to go in and it's going to change something in the genome, but it's a foreign protein and so it's possible that after you've made that edit, your body is going to raise antibodies against it. So if you did that, you wouldn't be able to make a second edit. Let's say someone has two genetic diseases, you would only be able to edit both genetic diseases simultaneously, you could never edit one and then come in a second time and edit the second disease because after you edit the first, they're going to raise antibodies against the CRISPR protein that you used to edit them the first time. So think that there's not really any sort of idea of making too many changes in the genome is going to cause any sort of toxic side effects, but there is this complication where we have a limited number of times that we can use this.

ANDI HORVATH
I'm Andi Horvath and our guest today is molecular biologist, Professor Jacob Corn. We're talking about the power of CRISPR gene editing technology here on Up Close. Jacob, do you see a future where the technology becomes so commonplace that we'll be using it for things like cosmetic purposes and that becomes the norm?

JACOB CORN
Editing for cosmetic reasons has a lot of barriers to it. I don't know if we're ever going to see it be used to, say, make people taller and anything like that for a variety of scientific reasons. Number one, we have absolutely no idea what makes people tall. There is actually a paper written about that a bit ago and it turns out that it's this huge number of genes that influence these things. So it's totally unclear whether the technology will ever be able to do that. I think also it's really hard to envision the use of something so invasive for something so trivial. People have talked about using gene editing for more science fiction type things. As an example, there are people talking about trying to send people in very long space missions, are there ways to

use gene editing to maybe increase radiation resistance to tolerate those missions, to reduce bone loss, things like that.

ANDI HORVATH
So enhancements to the human body to allow space travel.

JACOB CORN
Yeah, people have been talking about those sorts of things. That sort of stuff, at the moment, again, it's very science fiction and in some ways it's a little bit putting the cart before the horse. We're having these long arguments about should we do this thing that we can't do? I think it's important to look ahead, but if the technology is 15 years away from now, it's unclear whether our views of it will change in the next 15 years.

ANDI HORVATH
Jacob I notice that scientists are often cautious to say they're funding is for somatic cells and not the germ cell lines and germ cell lines, of course, means alternating the genetics of our offspring. So why can't we just edit out some diseases out of history altogether? This means editing the germlines and that would affect the future generations, permanently altering them. So can we and should we do it?

JACOB CORN
I think that question that you just raised, that's the key question: not can we, but should we. I think that theoretically, on paper, we might be able to do it. No one has done it yet, but theoretically we might be able to do it. The question really is, should we do it? Should we try? I think there are certain diseases where patients have asked for that kind of germline editing. A good example is Huntington's disease. In Huntington's disease, as generations progress, the disease actually gets worse from generation to generation. Your kids will have it worse than you did, their grandkids will have it even worse. So people say, let's stop this right where it is, let's not just treat every single generation over and over and over again. But I think that doing that has rightly raised a lot of ethical questions and, frankly, scientific questions among people. Ethical because now we're starting to mess with our own evolution and scientific because we really don?t understand human evolution all that well; we don't know why some traits are around, why others have been lost and so the idea of starting to introduce changes that will be passed down over time has people questioning do we really know enough to start doing this.

I think that for certain diseases, it is very tempting to want to do that, but frankly, for the vast, vast, vast majority of genetic diseases, there's no reason to do germline editing. For things like muscular dystrophy, sickle cell anaemia, any of these things, they're completely addressable in a somatic way. Now if you did a germline, it wouldn't be passed on to offspring, but there is a possibility, if your children had that genetic disease, they could get somatic therapy. So I think at this point we do need to stop, take count and say, we have the capability of doing somatic editing, do we want to expand that on to germline editing. In fact, very recently there were discussions from the National Academy of Sciences and the National Institute of

Medicine in the United States talking about germline editing, talking about whether or not it's appropriate. At the moment they've really called for, one, no federal funding to be used for it and two, let's try to put a moratorium, let's try to put a halt on it. There are some independent funders that have said, we will look at germline editing and part of the reason they've said that is in very certain cases. So I want to introduce the research uses of germline editing. We think of germline editing as this is the way that you're going to cure diseases and that's totally possible, but there are also certain scientific questions for human health that could only be addressable if asked in a germline setting. So for example, there is a woman in the UK who is trying to understand why so many in vitro fertilisations fail. A very, very large number of in vitro fertilisations just don?t work and it's very frustrating for the families that are trying to conceive that way and we have no idea why that is. So what this woman is trying to say is, well let's take some of these cases where they're failing and try to use gene editing as a research tool in those cases, not to take those edited zygotes to term, but they're already failing anyway, let's try to use CRISPR to ask why are they failing. We're not going to do anything with those zygotes, we're going to say what is going on scientifically and that will hopefully make IVF better.

Now I think if one were to put a complete ban on germline editing, that would be throwing up our hands and saying, we will never answer this question in this way. I think if we want to do that, we have to be comfortable with that outcome, we have to say we're going to draw a line in the sand and therefore we're never going to know. I think that there are a lot of people who are not comfortable drawing that line in the sand and right now what I think is happening is a lot of people are discussing very vigorously where the line is going to be. But I think that it's really important to think deeply about this because when we start talking about genome editing, it's very, very easy to conflate somatic editing and germline editing into the same sentence, into the same idea and I think in doing so, we start mixing in the murky, complicated ethical questions of germline editing with the very cut and dry single person editing of somatic. I think that's really important to take to heart because somatic editing does not get passed on, it cures just the person that has the problem and has none of the ethical quandaries. So I think when we start talking about regulations and ethical discussions and things like that, we need to be very careful about how we put those together and very careful about how we talk about these. We really need to think about them in a regulatory framework very, very differently and that's really important because we don't want to throw the baby out with the bathwater. If we make any type of ethical or regulatory considerations about germline editing, we need to make sure that we're not preventing cures for patients that are suffering right now from diseases that could be addressed with somatic editing, which would not be passed on through the germline.

ANDI HORVATH
Jacob my knowledge of CRISPR is now so much clearer, or crisper, if you like. Thanks for being our guest on Up Close.

JACOB CORN
Thank you very much. It's my pleasure.

ANDI HORVATH
We've been speaking about the power and the promise of CRISPR-Cas9 gene editing technology with Professor Jacob Corn, Scientific Director of the Innovative Genomics Institute at University of California Berkeley. You'll find a full transcript and more info on this and all our episodes on the Up Close website. Up close is a production of The University of Melbourne. Australia. This episode was recorded on 15 February 2017. Producer was Eric van Bemmel, audio engineering by Gavin Nebauer. I'm Dr Andi Horvath, cheers.

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