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#208: Stem cell therapy: The hope and the hype

VOICEOVER

Welcome to Up Close, the research talk show from the University of Melbourne, Australia.

SHANE HUNTINGTON
I'm Shane Huntington. Thanks for joining us. Over the last couple of decades stem cells have been touted as the key to treating a wide range of diseases, with advantages that exceed surgical repair or even organ transplantation; but work on stem cells, especially those derived from human embryos, has drawn significant public scrutiny. In many countries embryonic stem cell research is tightly regulated, and researchers have been forced to explore other research options. Such restrictions are not present worldwide and, in some countries, regulation has yet to catch up with the science. This can make it especially challenging for patients trying to navigate through the world of therapeutic stem cell technologies, both in trial phase and on the consumer market. To explore these issues and the technology itself we are joined on Up Close by one of the pioneers of stem cell research: Professor Martin Pera, program leader of Stem Cells Australia, and professor of stem cell sciences at the University of Melbourne. Welcome to Up Close, Martin.

MARTIN PERA
Thank you.

SHANE HUNTINGTON
Could you start by giving us a bit of an overview of what a stem cell is and why these particular cells have generated so much interest over the last two decades?

MARTIN PERA
Well, they're really two basic types of stem cells. One type of stem cell we cal pluripotent stem cells. And these can either be derived from very early stage embryos of they can now be created in the lab from adult cells, from patients, through a process we call reprogramming. And pluripotent stem cells are able to give rise to all the tissues of the body. The second class of stem cell is the tissue stem cell, sometimes called adult stem cells. These are stem cells that are minority populations in many adult tissues. They are, essentially, more limited in their potential; they usually only give rise to a few types. Both types of stem cells have two key properties. The first is that they are primitive cells that can give rise to more mature functional cell types like neurons or red blood cells. The second is that they can also divide to produce more stem cells. So stem cells provide a reservoir for tissue regeneration or repair. I think the excitement around pluripotential stem cells in particular has to do with the fact that they can be grown indefinitely in the laboratory and multiplied many times over to make more stem cells and that they can give rise to all the tissues of the body. So for the first time we've got an indefinitely renewable source of any healthy human tissue for use either in the laboratory or in transplantation medicine.

SHANE HUNTINGTON

You've been working at the stem cells, essentially, from the beginning, when you and others first discovered that you could, potentially, coax these cells down particular differentiation pathways. Tell us a bit about what that was like back then because I can imagine there would have been an incredible sense of enthusiasm with regards to the possibilities of such cells.

MARTIN PERA
Well, we were very excited. Of course, it was known since the 1980s that stem cells could be developed from the mouse embryo. Despite many attempts in the intervening years it proved difficult to derive these cells from other species. Then, in the mid-'90s, Jamie Thomson, in Wisconsin, showed that you could make pluripotent cells from the rhesus monkey embryo. And our laboratory, and a few others, set out to see if we could do this from human embryos. It was incredibly exciting when we first had some success, so that, indeed, we could make these cells and that they could turn in to human tissue-like nerves.

SHANE HUNTINGTON
What does it mean in terms of the progress of, essentially, combating a range of diseases at that point in time? It seems as though you had something that looked like it was an answer but, decades later, we're still sort of a fair way off.

MARTIN PERA
Well, at those early stages there was incredible promise and incredible potential. One of the most difficult things for us in the field was to convey that promise, and the excitement was not trying to claim that things were going to happen too quickly. To me, it's remarkable that only a little over a decade after human embryonic stem cells were discovered we're already seeing clinical trials of the first human embryonic stem cell derived products for conditions like macular degeneration, a very common cause of blindness. Now, that's remarkable because, as I say, it's only a little over a decade. Even in the drug industry - which is a well travelled paradigm for development of therapeutics - it's not unusual to have 10 to 15 years between the discovery and clinical trials. So I think this is quite remarkable. However, in many areas, we still have a long way to go for many applications.

SHANE HUNTINGTON
Martin, it's no secret that this area of research is very controversial for some people. About when did that start?

MARTIN PERA
Well, the controversy began almost from the original discovery because, of course, to generate these cells we had to use spare embryos donated by couples undergoing infertility treatment. And of course, that was the route of all the controversy. A significant minority were opposed to such use of embryos.

SHANE HUNTINGTON
What did that mean for the work you were doing in the lab? Did this, essentially, halt that work? Or did it send it into a scenario where you were unable to publicly talk about the successes you were having?

MARTIN PERA
Well, we were able to pursue the work and to publish our results, but I think, in a sense, the controversy did slow some of the research. It was hard to disseminate the technology in the early days. And it wasn't clear, in the early days, whether there would be full government support for this. So it took some time before there was public acceptance and a regulatory framework was put in place to enable the work to go forward.

SHANE HUNTINGTON
Now, in recent years the controversy surrounding embryonic stem cells seems to have waned somewhat. Is this your experience as well?

MARTIN PERA
I think there will always be a minority that are completely opposed to this work. However, I think that as we progress towards clinical trials and we begin to see potential benefits in man, a lot of that opposition will abate. I think also some of the controversy had been diffused by discoveries that we can now make pluripotent stem cells very similar to embryonic stem cells from adult tissues through this remarkable process of cell reprogramming. Although it's not yet clear that those will completely replace stem cells from embryos, we still need stem cells from embryos. Stem cells from embryos are the basis of the clinical trials, going forward. It may well be that these new techniques allow us to do a lot more without the use of embryos.

SHANE HUNTINGTON
Martin, a few years ago, around 2006, induced pluripotent stem cells were first discovered. How do these actually differ, in a biological sense, from embryonic stem cells?

MARTIN PERA
Well, the fundamental difference is that to make induced pluripotent stem cells we start with adult tissue. So we could take skin cell or a blood cell, essentially, from any patient and, through what is a remarkably relatively simple process in the laboratory, we can reprogram that cell back to a state similar to cells in the very early embryo. So we've taken an adult cell and, basically, turned it into something with many of the properties of embryonic stem cells. That is, the ability to turn into a whole variety of adult tissue types. So that is really a remarkable advance, and it gives us a lot more flexibility. We don't, obviously, have the ethical concerns that surround the use of embryos but, more importantly, it enables us to readily establish cell lines and develop wide banks of cell lines that will give us a better chance to match tissues to patients and get around issues of rejection. Importantly, now, we can also make pluripotent cell lines from patients with particular diseases. These may be simple diseases caused by one gene or diseases that involve complicated genetic susceptibilities. By making these cells we can then use these cell lines to study the disease in the lab. For instance, if we're interested in some type of heart disorder where the electrical conduction in the heart is disturbed by some mutation in a gene, we could take cells from that patient, turn them into pluripotent stem cells, turn those cells into heart cells and then study their properties and how the mutation affects the beating heart muscle.

SHANE HUNTINGTON
Now, you mentioned that it's a relatively easy procedure to convert adult cells into these stem cells. How exactly do you go about that in the lab? Can you talk us through the procedure?

MARTIN PERA
Sure. So in a typical example we might take a small biopsy from the skin of a patient and then we would grow cells called fibroblasts from that biopsy. These are cells that have, basically, been grown from skin biopsies for many years. They're a specialised type of cell, a connective tissue cell. But after we'd grow them up what Shinya Yamanaka discovered in Japan in 2006 was that by introducing a few genes, by putting a few genes into that cell - genes that are key to maintenance of embryonic stem cells and key to early development - introducing those genes can reprogram the adult cell back to an embryonic state. So these genes are like master regulators and they control the whole genetic program of early embryos and embryonic stem cells. And it turns out that if we put those genes into an adult cell, why, then we can switch

on that embryonic program again.

SHANE HUNTINGTON
This is Up Close, coming to you from the University of Melbourne, Australia. I'm Shane Huntington. In this episode we're talking about where we are with stem cells with Professor Martin Pera. When you grow these cells in the lab how long do they last?

MARTIN PERA
Well, we're still growing stem cell cultures that we first developed back in the late '90s. Those cultures are still perfectly normal. They can still turn into any type of body cell, and we distribute them to scientists all over the world, who continue to work on them. So the interesting thing about pluripotent cells is this - what we call immortality in culture: the ability to go on dividing and then producing more stem cells, essentially, indefinitely.

SHANE HUNTINGTON
Now, for a very long time we've been in the methodology of one size fits all medicine. As we move, now, towards the concept of personalised medicine, things like stem cells are being discussed a lot. Do you see their role as significant in the way in which personalised medicine moves forward?

MARTIN PERA
Well, I do, on two levels. First of all, because we can now readily make stem cell lines from a wide variety of patients with different genetic make-ups, that means that we will be able - to a degree, probably - to customise cell therapy to individual patients and to provide tissue that is a close match from the stem cells. But also - and this is a very, very important aspect that is sometimes overlooked - these new stem cell lines provide powerful research tools. So we could take a cell from an individual, turn it into a stem cell and then turn that cell into a whole variety of different types of cell in the laboratory. We could then study that individual's response to a particular drug or to a particular disease causing agent. So it enables us to look very closely - do human experiments in addition to laboratory - to look at the factors that affect, for instance, drug response of disease susceptibility. So I think, in that respect, this technology in the research lab will move personalised medicine forward.

SHANE HUNTINGTON
Now, assuming, here, there are two sorts of cells, essentially, that end up being used in these therapies - one derived from the person's own body, and the other is from, I guess, donors. How do you deal with rejection scenarios with the second of those two cell lines?

MARTIN PERA
Well, with cells from donors there are different approaches that are being envisioned. For instance, if we take the application of trying to treat macular degeneration - a very common cause of blindness - basically, we'll be inserting a little patch of stem cell derived cells at the back of the eye. Along with these cells we can deliver localised drugs to suppress the immune system; so just in a local way. In another application there's a company in California that's trying to treat diabetes. What they're going to do is actually encapsulate the eyelet cells from the stem cells made in the laboratory, in a small device that will then be implanted and may modulate the immune response. Of course, with induced pluripotent stem cells, now, we can custom tailor the stem cell lines so they're a much better match for individual patients.

SHANE HUNTINGTON
You mentioned macular degeneration as, I guess, a prominent area that's in clinical phase with stem cell

therapies. What exactly is happening there at the moment? How far have we gone? Are the results such that degeneration is being reversed?

MARTIN PERA
So the treatment for this condition is being developed in a number of places. It's been developed by my colleagues in California. It's been developed in England and also there's a company in the United States that's pursuing this. Where are we? We know that we can make the [right] cell type that is destroyed in this disease. It's a cell type called the retinal pigment epithelium, which is very important for the function of the photo receptors in the eye. So we can make the right cell type. We know that that cell type is functional. We know that it works in animal models. Where we are now is that there's at least one clinical trial going on. It's in what we call phase 1 trial, which is, really, just to look at safety. The first couple of patients were published in early 2012, I think, in the journal, Lancet. And what that study showed is it's too early to know whether treatment is effective, but it does show it's certainly feasible and, apparently, safe. And I think within a couple of years' time we will see more trials, more patients and we'll begin to get a picture of whether this treatment is truly beneficial. Often, the animal studies are very encouraging but, obviously, it's more complicated to treat a disease in a human population than it is in a very controlled setting in a laboratory animal.

SHANE HUNTINGTON
When you talk about safety with these trials can you unpack a bit what sort of things the patient is at risk to with regards to stem cells?

MARTIN PERA
Well, I think with pluripotent stem cells - whether they're embryonic stem cells or induced pluripotent stem cells - one of the real concerns has been tumour formation. And if we were just to implant the stem cells themselves they would form a tumour at the site of implantation, called a teratoma; that's an inappropriate growth. Also we know that sometimes, even if we implant more mature cells that are partially differentiated, we can get different types of tumour forming. And that's a real concern. The way around that is to make sure, through various techniques, that what we are injecting into the patient is very well defined and very, very pure. And if we do that, we can ensure safety. Of course, there's lots of tests in animals that we do over a long period of time, but one of the challenges here is, of course - unlike a drug, which may persist in the body for a few hours or a day at the most - these cell therapies are meant to stay there for, in many cases, a good portion of the patient's life span. So we have to be, I think, quite careful in what we do. Always we have to balance concerns for safety against possible benefits for the patient and how big is the risk against the potential benefit. It depends on the condition.

SHANE HUNTINGTON
Martin, why did we choose the eye? When I think about the body, I guess, things like heart muscle and other parts of the body seem a bit simpler than aspects of the eye. Why, specifically, has the eye been chosen for these first clinical trials? Why are we not at the same stage with some of those other organs that are, potentially, more concerning?

MARTIN PERA
Well, macular degeneration is, in a way, a very, very special case for a number of reasons. In the first place we know that we can make the cell type that is missing - the retinal pigment epithelium cell - and that it's mature and functional. In many other applications - let's think about treating heart attacks - we can make heart muscle from stem cells, but it's not fully functionally mature. It's more like a foetal cell and not so easy, really, to replace function in the adult yet. The second aspect of the eye that's interesting is that

we really don't need to make very many cells to treat an individual patient. It might be of the order of 100,000 cells or something like that; whereas, for other applications, we might need to make billions of cells. A third aspect is that there's fantastic technology for imaging the eye and the graft and monitoring how the graft is doing; whether it's actually treating the disease and whether it's going, somehow, off the rails. And in many other cases it's really difficult to know what happens to stem cells that are introduced intravenously or into a tissue such as the heart. And finally, in the eye, we can handle the question of rejection just for the localised immunosuppression rather than systemic so we don't have so much toxicology associated with it. So the eye is, really, a very, very special case and affords, I think, a good, early test of the potential of these therapies.

SHANE HUNTINGTON
I'm Shane Huntington. My guest today is Professor Martin Pera. We're talking about stem cells and regenerative medicine, here on Up Close, coming to you from the University of Melbourne, Australia. Martin, can you give us an idea of what aspects of stem cells you're investigating in your laboratory at the moment?

MARTIN PERA
Well, my laboratory, for a long time, has been interested in human pluripotent stem cells. We've been studying, really, some of the factors that control how those stem cells multiply and how they begin to turn into specialised cell types. It's really about understanding what makes those pluripotent stem cells tick, but that's incredibly important. If you think about producing a large number of cells - mature cells in pure form to great patients - you have to have pretty strict control over the stems cells and what you're doing with them. So that's one aspect. Here at the University, in the Melbourne Brain Centre, we're particularly interested in determining human pluripotent stem cells into precursors of nerves. And in particular, we're interested in using these systems to study the human cerebral cortex. That's the part of the brain that is uniquely human; the seat of consciousness and many other higher functions - difficult to study in experimental animals for that reason. Now, for the first time, we have a tool in the laboratory. We can study human brain development. And of course, now, it's increasingly appreciated that a number of important diseases, like schizophrenia, autism and epilepsy, have their origins in brain development, but it's been very difficult to study. Now we have the potential to at least try and do that, so we're very excited about that.

SHANE HUNTINGTON
When you talk about the potential to study these diseases are you referring to the idea of actually removing cells from the patient and then turning them into these stem cells and following that procedure so that you have, essentially, the model of the person outside the patient in the lab?

MARTIN PERA
That's exactly the idea. I think that's what a lot of the excitement is about and, particularly, if you think about diseases that might have had their origin early on in the development of that patient's brain, with induced pluripotent stem cells we can recapitulate some of those early events and, hopefully, study what went wrong and how better to deal with it. So it's very, very exciting, but it's not a simple matter because whilst it's fairly easy to take cells from patients and make induced pluripotent stem cells from them, we have to then be able to make the cell type that's affected in the disease and we have to also show that we can recapitulate the disease in cell culture. And that's not always simple because, of course, many diseases are complex. They involve multiple cells in a tissue, many interactions, they occur after many years of ageing. So this modelling of diseases - whilst it's very promising - there's an awful lot of work to do, in many cases, to get it right.

SHANE HUNTINGTON
Do you think we'll get to a position where we should all be, essentially, banking samples of ourselves while we're healthy to help with this process?

MARTIN PERA
You know, that has been suggested. I think there will be banks of induced pluripotent cells generated. I think there's a common misconception that we will be making specific cell lines from individuals to match that particular individual. It's a great idea, but it's really an enormous amount of work, and testing the cells and making sure they can turn into what we need and making sure that it's safe is really, logistically and in terms of cost, quite a substantial undertaking. So I think the more likely scenario is that we will make banks of cell lines from diversely genetic backgrounds that then provide reasonable tissue matching for individual patients. Really, the number of cell lines we will need to do that may not be so enormous. It may be hundreds or thousands, but not tens of thousands or hundreds of thousands.

SHANE HUNTINGTON
Martin, I'd like to talk about the community's view of stem cells for a few minutes. Do you believe that the community has unrealistic expectations on what sort of therapies will be available today, tomorrow, in the very short term?

MARTIN PERA
The question of community expectations has been, from day one, a real challenge for this field. It's hard to get across the potential, but also how complicated it is to get to some of these end points. Unfortunately, I think, there are clinics now - overseas and, perhaps, even here in Australia - that are offering so-called stem cell treatments that are unfounded and unproven and, really, have no basis in science. I think because the public has heard so much about the potential of stem cells some of these less ethical operations can exploit some of the misunderstanding. This is a development that's of real concern to us in the field.

SHANE HUNTINGTON
Is there any actual evidence at the moment that any of these ad hoc therapies have had positive results?

MARTIN PERA
I think, with a lot of these stem cell clinics that promise simple, one shot treatments for a whole range of diseases, the evidence is simply anecdotal. There is no hard, clinical data. It's really patient testimonials. The difficulty with individual patient testimonials is that it's very, very hard to know whether the treatment was actually responsible for the improvement that the patient may have observed because, of course, many diseases have a variable course. So we have to really study, in the context of a trial, these new treatments over some years - in many cases with large numbers of patients - to really be sure they're working. That's what the public would expect. If you go to buy a medicine - your doctor gives you a prescription -you want to go to the chemist and be sure, at least, what's in the pill is what it says on the label and that there's a reasonable chance that it might do you some good and a very strong likelihood it won't do you any harm. That requires years and years of testing in the right settings.

SHANE HUNTINGTON
Martin, just finally, what do you think will be the next organ or body part of choice to be attempted in terms of these stem cell therapies?

MARTIN PERA

So I think there are some very interesting prospects. There's a type of stem cell from adult tissues, called mesenchymal stem cell, which, while limited in its ability to give rise to - it really gives rise to only a few cell types, but it does seem to have an interesting potential to go to sites of injury and enhance the body's own repair process. So these mesenchymal stem cells are now on trial for a whole range of conditions in which they're not really replacing damaged cells, but modulating the body's own repair. In terms of the embryonic or pluripotent stem cell field I think, fairly soon, we will see more trials in macular degeneration. I think that we have a reasonable chance of seeing trails in diabetes soon. I think that there's renewed interest in cell therapy for Parkinson's disease. This was one of the early targets that people were very excited about. It took much longer than we thought because it was actually a case of learning how to make precisely the right type of nerve cell that's missing in that disease. But we know how to do that now. So I think that's another exciting area. Other areas, frankly, are further off. I think replacing heart muscle - whilst we know we can make a cardiac muscle from pluripotent stem cells, the challenge there is, really, getting the tissue we make to mature so it's got all the functional capability of adult heart cells. And also how do we integrate it into the adult heart? If you think about it, it has to not only sit there; it has to beat in unison with the patient's own muscle and be electrically coupled and everything else. These are real challenges.

SHANE HUNTINGTON
And Martin, with regards to the technology and how it's changed over the last decade or so, how has that influenced the work on these stem cell therapies? What sort of things to do you need, technology-wise, to push these along in the future?

MARTIN PERA
So I think there have been enormous improvements in our understanding of the basic biology of these cells. We've learned how to grow them much better. We can scale up the cultures and getting much better at turning them into the types of cells we need to study and treat disease. I think there is still some way to go in terms of learning how to mass produce particular types of cells. I think the induced pluripotent stem cell discovery of Yamanaka was an enormous breakthrough, but we still have an awful lot to learn about those cells and how to cultivate them in a way that they don't acquire genetic lesions that might give rise to cancer et cetera. The other thing I think we'll have to see is some degree of automation of all this technology so that we can do a lot of this work on a medium to high throughput scale. That's work that is going on here and elsewhere. So I think the prospects there are pretty exciting, but still some way to go.

SHANE HUNTINGTON
Professor Martin Pera, Program Leader of Stem Cells Australia, and Professor of Stem Cell Sciences at the University of Melbourne, thank you for being our guest on Up Close today and talking about the promise and the reality of stem cell research.

MARTIN PERA
Thank you. It's been a pleasure.

SHANE HUNTINGTON
Relevant links, a full transcript and more info on this episode can be found at our website at www.upclose.unimelb.edu.au. Up Close is a production of the University of Melbourne, Australia. This episode was recorded on 11 July 2012. Our producers for this episode were Kelvin Param and Eric van Bemmel; associate producer, Dyani Lewis; audio engineer, Gavin Nebauer. Up Close was created by Eric van Bemmel and Kelvin Param. I'm Shane Huntington. Until next time, goodbye.

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