A conversation with Alan Colman, Singapore

"Only the Tip of the Iceberg"

Alan Colman, one of the "fathers" of Dolly, the first cloned sheep, talks about the importance of cell reprogramming, the promises of stem cell research, why he left Europe for Singapore and cheating in science.

Lab Times: You were part of the team that cloned "Dolly", the world's first sheep created from an adult somatic cell. That was in 1996 and a scientific sensation at that time. If you now look back on the last ten years, what was the most important discovery in the life sciences for you?

Colman: There are, of course, many different answers to this question, depending on your own areas of interest and research. From my own perspective, I'd say that the discovery of induced pluripotent stem cells (iPS) by Shinya Yamanaka was certainly one of the biggest and most surprising breakthroughs. There is of course an interesting connection between Yamanaka and our research. We managed to render a cell pluripotent in a very indirect way through nuclear transfer, whereas ten years later, Yamanaka was able to show that many, if not all, somatic cells can be reprogrammed just by four additional factors and without taking the nucleus out.

Did Yamanaka see this connection?

Colman: Yes. Yamanaka himself said that Dolly, which was a surprise even for the people involved, gave him optimism that the impossible can be done and a total reprogramming of an adult somatic cell could work. His work was resuscitating a field that had gone as far as it could with nuclear transfer. Yamanaka did the impossible. And now, I've jumped onto the back of what he did. It is an iterative thing.

Before moving to iPS you were doing research with human embryonic stem cells (ES)…

Colman: …yes, and that was tough.

Because of the political and ethical debates involved?

Colman: No, not in my case. In the countries I chose to work – in the UK and then in Singapore – there was a permissive legislation. The toughness lies in controlling the differentiation. And that is also the problem with pluripotent stem cells. It is one thing to reprogramme cells but completely another thing to take those reprogrammed cells – whether they are ES or iPS – and re-impose a new differentiation-process on them. It is not clear, in any case, that we can make an adult cell out of an embryonic cell.

Do you still have to do research with ES? Or has that become unnecessary?

Colman: We cannot be absolutely sure that iPS and ES are identical, although it is becoming clearer each day how identical their functional properties are. But there are still some residual transcriptional differences and we do not know whether they are important or not. In our lab, we use ES now as controls and reality checks for iPS-cells. But we don't make any new ES.

Is there any more need for producing new ES lines?

Colman: If we get cell therapy going then we would need clinical grade pluripotent cells. That hasn't been achieved yet for iPS. I am equivocal about that. In August last year, the US biotech company Geron was forced to delay its first human study for treating victims of spinal chord injuries due to the FDA's concerns after it had granted permission to conduct the trial. The reason why I mention this is that Geron took an existing "dirty" ES-line and validated it for clinical use. So my feeling is, as the future unravels, you'll have to make a stronger and stronger case for new ES lines and to be allowed to use new embryos. In general, I think that iPS are going to take over.

"The toughness lies in controlling the differentiation."

Where do you see the most important areas of application for iPS? Will they be used as a model to study diseases?

Colman: I'd like to think it would. But we don't know yet how good they work as models to look at the early stages of many human diseases. We still don't know whether this is a flawed or a good concept. It might be that it is flawed for some diseases but good for others. The scientific community also wants to use them to provide unlimited quantities of cell-types for drug-screening and drug discovery. So the concept is that you would create a lot of motor neurons with genetic lesions and you could then test drugs to arrest that disease. To me, that is a really important area at the moment. But we still have to try a lot and see how successful it is going to be. One other area of use of iPS is the general area of reprogramming. But I am not going to go down that way.

Why not?

Colman: Because that way has its problems. For a description of the Yamanaka type of reprogramming, I use the metaphor of going down the Empire State Building with the differentiated cell at the top – and you want to go down to ground zero. Of course there are many ways to go down. You can parachute down, you can climb down or you could take an elevator. I predict that reprogramming is a very crude way and that there are many routes. And looking at the reprogramming, it might not be that informative to look at the exact route. What is very interesting, though, is that some recent data shows that if you inactivate those tumour suppressor genes, then it makes it incredibly easy to reprogramme cells.

Why is that so interesting?

Colman: There you can see a link between cancer and stem cell research most clearly. As you get older these protective genes you have are mutating and you can get cancer. And there might be a link to reprogramming where this is happening *in vitro*. And that finding might be useful for

future cancer therapy. Obviously, the areas of stem cells and cancer have been moving much closer together over the years and are rapidly coalescing. It is still controversial, though, and the cancer stem cell hypothesis is not all singing all dancing. It does not fit every case. But as it seems the pluripotent state is so poised between normal development and cancer.

"I don't believe in personalised therapy."

What about creating tissue out of iPS? Or even cell therapies?

Colman: Cell therapy is still a very tough area. I spent seven years on it. It was really in some ways very unrewarding because it is a much greater challenge than creating Dolly. That will have the same problems as you have when creating tissue out of embryonic stem cells. I think it is a worthy challenge. But in terms of cell therapy you not only have that challenge but many more challenges, that is putting the cells into people, immunological issues – all potentially solvable, but I think that it's still a long way away.

Any guess how long that might take?

Colman: That depends on the area. For diabetes and heart restoration, it will be many years, if not decades. But in simpler indications such as skin problems in the eye, we can expect progress quite soon. I have a colleague in London who has been sponsored by Pfizer now to bring cell therapy into the clinic in the next two or three years. This is to cure age-related macular degeneration that many people experience when they get older and when the retina of the centre of the eye deteriorates.

What about the costs of these kinds of therapies?

Colman: I have always felt that personalised therapy, that is therapeutic cloning etcetera, was never going to be a runner. I think that the cell therapies will have to be generic, so that you can apply one type of preparation to many people. I don't believe in personalised therapy.

Mapping the field of stem cell research it seems that the US and East Asia – Japan, China, Korea and Singapore – are doing very well and Europe is lagging behind. Is that a correct impression?

Colman: Yes. Europe is partly lagging behind because the whole ethical debates on human embryonic stem cells polarised many countries here, especially Germany, Austria and Italy. But stem cells are not just embryonic stem cells or iPS cells. There is a lot of interesting work with adult stem cells and, of course, hematopoietic stem cells are very important in the sense that you have therapies already. And they were not affected by this debate. But I think the countries that have a more permissive legislation also have more investment in the whole stem cell area. Even Spain, which is a catholic country, was happy to endorse the use of human embryonic stem cells.

You moved to Singapore a few years ago and then you divided your time between London and Singapore. Are you planning to come back to Europe?

Colman: No, to the contrary. I have resigned in England and am now full time back in Singapore because the resources there are just so much better. I had started to share my time between London and Singapore two years ago; London is a fantastic city for social reasons and theatre. But I decided that, professionally, it wasn't helpful to travel so much. And it is not green.

Your field of research was overshadowed by one of the biggest scandals in recent history of science – the case of Hwang Woo-suk who was punished quite mildly last year. How exceptional is his case?

Colman: I think that frauds like the one of Hwang are only the tip of the iceberg. It is not just that type of obviously major fraud that is the problem for science. There are many more subtle ways of cheating, and not just cheating. Think of guest-authorships. There are many levels of betrayal. And we have to remember that a lot of science is funded from the public purse and that the public are rightfully horrified when they hear about some of the things that go on. This could have a very bad impact on the future funding. In the Roman or British law you are innocent until you are proven guilty. For scientists this might have changed in the public perception.

So how can you change this image and, more important, restore research integrity?

Colman: First of all, we have to confess that there was always cheating in science. Just think of Gregor Mendel, who was accused of massaging the data, although he clearly was right and his research was important. Nowadays, it is essential that there is more regulation and policing in science. But there is a dilemma.

And that is?

Colman: If you get too bureaucratic and create too much legislation, this will impede the progress of science. With more regulation there will be less bad science but there also might be less science in total. Therefore, society will suffer because things don't happen soon enough. It is going to be a delicate balance and it is important for scientists to be more alert to problems in their own lab. Sometimes these things are happening even in your own lab and there is a responsibility for the principal investigator. And sometimes even principal investigators cheat.

Are offices of research integrity a good way to cope with these problems?

Colman: Yes and no. Obviously it is good to be doing something. But as you can see in the US, with the case of David Baltimore and Thereza Imanishi-Kari, it can take a huge time to investigate just one case. And that's the problem. These cases can tie up scientists for a long time and there is always a sword hanging above them.

"Sometimes even principal investigators cheat."

What about courses on research integrity for young scientists?

Colman: Yes. That has to happen and that is happening. Such courses are becoming obligatory for PhD students in the US and we also do this in Singapore. But of course this will not stop the cheating. My wife teaches one of these courses and the problem is that you show how it works. That is a dilemma that in giving these courses you give clues on how to do bad things. Of course we also test essays for plagiarism, which is thought to be minor to data manipulation in research, but it has the same motivation: a desire to deceit usually for personal gain, for money, for the career, or whatever. It is really human psychology at the end of the day.

INTERVIEW: KLAUS TASCHWER

Alan Colman is currently a Principal Investigator in the A*STAR Institute of Medical Biology and also Executive Director of the Singapore Stem Cell Consortium. From 1987 until March 2002, he was research director of the company PPL Therapeutics in Edinburgh, UK. From 2002 to 2007, he worked for the Singapore-based company, ES Cell International.