The birth of cloning: an interview with John Gurdon

Sir John Gurdon used nuclear transplantation and cloning to show that the nucleus of a differentiated somatic cell retains the totipotency necessary to form a whole organism. Here, he discusses model organisms, the future implications for his early work on medicine and his thoughts about scientific publishing.

Since our introduction to Dolly the sheep in the 1990s, it seems somewhat logical that a whole organism can be made from the nucleus of a mature somatic cell. However, the idea defied dogma at the time when John Gurdon, then a graduate student, first proved that an entire tadpole could be made from combining a denucleated embryonic cell with a somatic cell nucleus. From this discovery, cloning was born and he has extended his research to the understanding of mRNA translation and gene regulation. John Gurdon was knighted in 1995 and has had an institute named in his honour (the Gurdon Institute) for his unique contributions to science.

When you designed your nuclear transfer experiments, were there specific features that attracted you to the South African clawed frog, *Xenopus laevis*, as a model organism?

There were indeed. The only previous work of this kind had been done with an American frog called *Rana pipiens*, which has the disadvantage that it only lays eggs for one or two months each year, usually in March or April. You cannot obtain their eggs at other times of the year, whereas Xenopus will lay eggs whenever you inject mammalian hormone into it, at any time of year. So, you have five to ten times more material with Xenopus than with other kinds of frogs. The availability of material is a good reason for choosing an animal.

One further point is that the Rana frogs take about 4 years to reach sexual maturity, whereas the Xenopus frog reaches sexual maturity at between 6 and 12 months. With Xenopus, you can bring animals to sexual maturity quickly and it's realistic to maintain frogs with mutations. Those were the two main reasons for choosing Xenopus, and using it increased work efficiency enormously.

When choosing a somatic cell nucleus for experiments that would determine its capacity for creating a whole new organism, you used a tadpole intestinal cell. Was there a specific reason for thinking that this cell nucleus would be totipotent and work well in this experiment?

There was a good reason why I chose it. I started work with the tissue called endoderm in the embryo. The endoderm happens to have very large cells, making it convenient for this kind of work, and I kept finding that I could get normal development of many tissues from these cells – even when the endoderm cells were close to being differentiated into gut epithelium. Having followed that lineage, it made sense to go on to the intestinal epithelium, which is what the endoderm cells go on to form. It was a tissue of choice because the convenience of large cells makes it easier to do the experiments and, furthermore, the intestinal epithelium is a continuously dividing cell type and that's more appropriate for these experiments compared with cells which cease division altogether. For all these reasons, there was a good rationale for choosing the intestinal epithelium for this work.

Your early cloning experiments made a big splash and ignited some initial controversy. Do you feel like you had to take a calculated risk to achieve your eventual success?

You're right that the work was strongly criticised at an early stage. That was really because it came to the opposite conclusion from that reached by Briggs and King who first developed this methodology. Understandably people were critical. Briggs and King reported that, in *Rana pipiens*

frogs, eggs receiving transplanted nuclei from a more mature cell type could not differentiate owing to the 'specialised' properties of the nucleus [King, T. J. and Briggs, R. (1955) *Proc. Natl. Acad. Sci. USA* **41**, 321-325]. After all, I was only a graduate student at the time and, as a graduate student, you shouldn't contest the results of famous people in the field. There were understandable reservations.

However, there was not too much risk incurred in that particular bit of work as we had the huge advantage of a genetic marker, which was not available in other species. This was important, because if you transplant a nucleus and get a normal animal out of it, you really want to prove beyond doubt that the animal has come from the transplanted nucleus and not from the resident egg nucleus, which, occasionally, might not have been removed.

Do you think that cloning and our understanding of stem cells will directly influence human health?

Yes, I think there are two ways in which it might. One is that when you carry out a nuclear transfer experiment, moving the nucleus of a somatic cell into an egg, there is a remarkable re-programming effect. You rather dramatically reset the pattern of gene expression of the somatic cell nucleus,

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changing it from the specialised type of the differentiated cell back into the stem cell type of an embryo. So in effect, you are deriving stem cells from an adult cell and if one thinks of that in mammalian terms then you can take, for example, a skin cell (or any other kind of adult cell) and create embryonic cells from it. By applying Martin Evans' famous embryonic stem (ES) cell methodology, these cells can then be expanded into a large number of cells and, subsequently, directed to a cell type of choice. This is a potential route towards cell replacement. I should emphasise that this procedure gives you the same genetic type as the source of the donor cells. They call it person-specific cell replacement.

The second area where this technology might influence human health is through the creation of disease models for testing, which is very relevant to DMM. If you have a diseased individual, you can derive proliferating cells from a diseased somatic tissue. This nuclear transfer ES route allows you to create a large number of cells in culture, which can then be analysed to determine what is wrong with them and possibly whether there are any agents available that can alleviate the problem. So, this technology can influence models for disease and perhaps provide a route towards trying to alleviate disease.

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What do you believe the future impact of model organism research will be on medicine and patient care?

I think that there is a great future for model organism research because it's not always easy or satisfactory to do everything with human cells. Often, it's better to choose the most tractable system to answer a question and then switch to humans. One might work with mice or frogs or something else, to find important processes or genes. Once you've found the genes or their products in a model organism, it's not so difficult to find the equivalent human ones. So, there's a great logic in working with whatever organism or system is most tractable. I could quote the famous case of Rita Levi-Montelcini and Stanley Cohen who discovered the nerve growth factor (NGF), which is of great importance. They received a Nobel Prize for it. The work was actually carried out through a route of understanding nerve fibre growth in chick embryos – the work then focused on snake venom, followed by rats and higher mammals. So, this is a very good example of choosing the most tractable system and then switching to the one of most practical relevance after you've more or less answered the outstanding questions or identified the important molecules.

The Wellcome Trust/Cancer Research UK Institute for Cell Biology in Cancer was renamed in your honour and is now the Gurdon Institute. Are there any particular qualities that you, and the Institute, look for in young investigators when recruiting new faculty.

We particularly like any new group to have something in common, scientifically, with other existing groups. For new group leader positions, we purposely select people who have an obvious overlap of interest with at least one, and preferably more than one, of the groups in the Institute. What we do not do, is find that we have nobody here working with yeast or fish or something else, and then attempt to fill a gap. A biochemist might say 'we don't have anyone working on lipid metabolism so we'll choose a lipid biochemist next time round'. We do the opposite.

Of course, we look at any very good candidates, but we are particularly attracted to ones that would connect with a couple of other groups who are interested in a somewhat related area. We purposely choose people with an interest in ongoing work in the Institute because, in most cases, work progresses particularly well when you have collaborations between people.

Within the Institute, how do you facilitate collaboration rather than competition?

We don't really experience significant competition because it is not a very large institute. We have 15-16 groups and all of us realise that our viability depends on the success of the Institute. People are not competing against each other, but rather against the rest of the world to try and make a mark.

However, there's an additional comment that's not as trivial as it sounds – you need a good tearoom. The best example of this is the Medical Research Council Laboratory for Molecular Biology, Cambridge, England. It is uniquely famous, having produced some 15 Nobel Prize winners, despite being quite a small institute. They have a lovely room where people like to go for their coffee, tea or lunch and talk over experiments quite extensively before they actually plan or do them. So, to have a place where people like to communicate is, in my view, a great asset and not as trivial as it sounds.

You are the Chairman of the Board for The Company of Biologists (COB). Why do you choose to invest so heavily, in terms of time and effort, in this scientific publishing group and charity?

I am a keen supporter of COB because scientists own the company. Scientists are the directors of the company and they determine policy entirely. Because of this structure, it is a charity. The scientists who kindly give their time to managing the company, many of them highly distinguished researchers, give their time for free because they feel they are serving the community. The profit from the journals that we publish goes back into science in the form of grants and awards. I would like to see this as an ultimate model for all scientific publishing. At present, the big-journal-owning businesses, of course, take a healthy profit. You could view this as a case where the scientists are the ones who do the experiments, submit their papers to the journal, referee the papers and get the grants to do all of this – the scientists do everything – and the profit goes to someone who is not a scientist. My view is that it would make the best sense if the major scientific journals were in fact owned and run by scientists for the benefit of the scientific community. That is what the COB is doing. So many of us are keen to support it for that reason and, indeed, that is how it came into existence in the first place.

DMM greatly appreciates Sir John Gurdon's time and willingness to share his personal story about how cloning became possible and how this important technology might impact patient care in the future. We are pleased to present his story as a DMM Model for Life.

Sir John Gurdon was interviewed by Kristin Kain, Associate Reviews Editor for DMM.