Sir John Gurdon: Godfather of cloning

John Gurdon isn't giving up on nuclear transfer despite the developments in inducible pluripotency.

Sir John Gurdon's famous frog cloning experiments of the 1960s and '70s answered a question that had been hanging over cell biologists since before the turn of the century: are the cells of an adult organism genetically identical to the fertilized egg from which they are derived? Briggs and King in the early '50s suggested that cells' genetic material is irreversibly altered as they begin to differentiate. But Gurdon showed that this was not the case. By transferring the nuclei of adult frog cells into enucleated eggs, he obtained cloned adult frogs (1, 2).

"As I was obviously deemed to be so bad at science, I applied to Oxford to do classics."

These experiments, together with the more recent cloning of Dolly the sheep, revealed the potential of nuclear transfer for cell replacement therapy. The potential would be even greater if cells could be reprogrammed directly, without the need to transfer nuclei into eggs—a scant resource in humans. To this end, Gurdon has spent much of his career deciphering the molecules and mechanisms that the egg uses to "rejuvenate" nuclei (3).

In 2006, Shinya Yamanaka from Kyoto University reported that adult fibroblasts can be reprogrammed into embryonic stem cells by stably transducing them with four factors (4). In a recent interview, however, Gurdon explained that there is still much to be learned from nuclear transfer, as it remains the most efficient way to reprogram a nucleus.

FROM LATIN TO LABORATORY

I understand that at school you were strongly advised against becoming a scientist.

Yes indeed, that's correct. I did one semester of biology, and then the master wrote a report that said, "I believe Gurdon has ideas about becoming a scientist. On present showing, this is quite ridiculous. If he can't learn simple biological facts he would have no chance of doing the work of a specialist, and it would be a sheer waste of time both on his part and of those who would have to teach him." That was a pretty crippling introduction to biology.

You remember the report by heart?

I keep it above my desk for my amusement.

What made you defiant enough to study science then?

As I was obviously deemed to be so bad at science, I applied to Oxford to do classics. But then the admissions tutor got in touch with me and said, "I'm delighted to tell you that we can accept you—on two conditions. One is that you start immediately. The second is that you do not study the subject in which you took the entrance exam."

And so you opted for zoology?

Yes. Later in life, I happened to discover the person responsible for admissions. He told me that he'd made a mistake and was short of science students. He had 30 empty places in the college. So he'd gotten in touch with extra people, including myself. I was a bit lucky there.

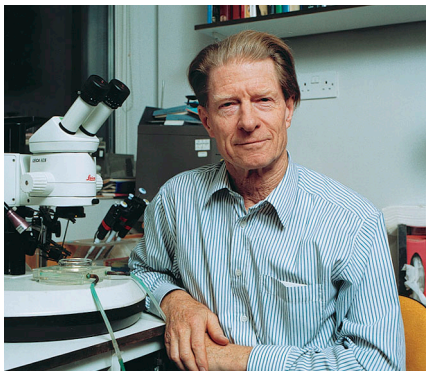
My kind parents could see that I really was interested in biological sciences. So they arranged for me to have special teaching to make up for what I'd missed.

Clearly, it paid off, because you fell in love with the subject.

I always had been very interested in the subject. It was just that I couldn't handle the teaching in school. The system didn't suit me. We had no textbooks—this was after the war—and we had to remember facts and make notes. If you weren't good at that, you couldn't possibly pass any tests. And I wasn't and didn't.

But once you were at Oxford, you flourished and decided to stay on for a Ph.D.

Yes. But actually I first applied for a Ph.D. in entomology, which had been one of my hobbies, and they declined me. That was lucky for me, though, because instead a wonderful teacher in developmental biology offered me a place. And that's when things got underway.



ANNUAL REVIEWS

Sir John Gurdon

That's when you got paired up with Michael Fischberg and the nuclear transfer experiments began?

Yes, that's right. Michael was my supervisor. Wonderful man.

But after your Ph.D., despite all your success with nuclear transfer, you headed off to Caltech and studied something completely different. Why?

Michael said to me, "There's no point in doing a postdoc in exactly the subject that you know how to do. You should do something completely different." He happened to know George Beadle of Caltech, and through this connection, I was offered a postdoc position.

I worked with a very bright, young, new professor called Bob Edgar on bacteriophage. But I could never make these phage work properly, I couldn't handle them at all. After a year of trying, I gave up and went back to working with embryos, but with the great benefit of having had a year's education at Caltech. It was good to take that year, and I now encourage my own students to consider doing something different for a while to give themselves a new point of view.

Text and Interview by Ruth Williams
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RETURN OF THE NATIVE

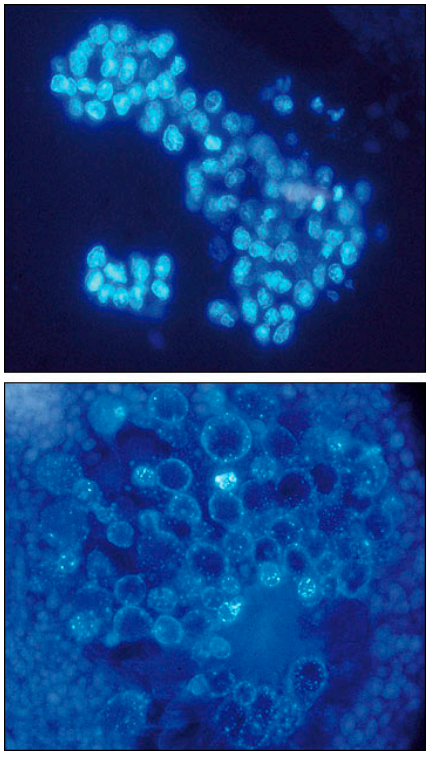
Was it an easy decision to come back to England after Caltech?

It was a matter of amazing fortune. My old boss, Fischberg, accepted a professorship in Geneva, leaving his post empty, and the head of the department decided to offer me the position at a lower level. It suited me very well to come back to this country.

You moved to Cambridge in 1971, and then in 1989 you started the Wellcome/CRC Institute. How did that come about?

I'd been at the Laboratory of Molecular Biology with Max Perutz for over ten years when Professor Horn at Cambridge University offered me and my colleague, Ron Laskey, a floor to start up a molecular embryology unit.

That seemed to go well, and then the Cancer Research Campaign, who provided my funding, asked if we would be interested in expanding. We said, "Yes, that would be nice. Ideally we'd like to have a small research institute." They said, "That's good, but we can't pay for all that." But by good fortune, the Wellcome Trust was willing to collaborate with CRC to fund an institute.



HeLa cell nuclei (top) appear quite different after being reprogrammed inside a frog egg (bottom).

In 2004, the institute was renamed after you. How did that feel?

That was an odd circumstance. When we started our institute, we called it the Wellcome/CRC Institute, and that was fine, but then the same combination of sponsors started up other institutes around the country, also called Wellcome/CRC Institutes.

It was very difficult to identify one from another. The view was that it would be better if we had a particular name to differentiate us. The director at the time was Jim Smith, a very fine director, but there were so many Smiths in the world that it didn't seem a very helpful name. So they looked down the list, and they saw a rare name, and thought, "Well, let's take that one, that'll do."

It was a bit of luck. There's no doubt about that. But if you're wise, you gratefully accept it and take advantage of it.

CURRENT RESEARCH

Now that it's possible to convert adult cells into embryonic stem cells using just four factors, where does that leave nuclear transfer?

Nuclear transfer is still the most effective way of deriving embryo cells from adult cells. The very clever Yamanaka approach works, but only about 1 in 5,000 cells will make the transition.

My own view is that the most successful route would be to understand how it is that an egg can reprogram somatic cell nuclei with such high efficiency. An egg has a way of rejuvenating a nucleus that no other cell has. If we knew how the egg does it, we could combine that knowledge with the IPS (induced pluripotent stem cell) routes and make it more efficient.

This might also circumvent the need to add genes to cells, since there is some concern as to where the incoming genes land. If you can reprogram the nuclei the way the egg does, leaving the genome completely the same, that would be ideal.

I always thought nuclear transfer was terribly inefficient.

To get a sexually mature adult animal this way is very inefficient. For the purposes of therapeutic cell replacement, however, an adult animal is not what you want.

You're trying to derive one kind of cell—a heart or brain cell—from another, easily accessible cell—a skin or bone marrow cell. And the efficiency with which an egg can cause a complete switch, such as from skin to muscle, is something like 30%, compared with 1 in 5,000 for the IPS route. You would expect this, because every time an egg is fertilized, the sperm, which is a highly specialized cell, is turned back into an embryonic cell.

"An egg has a way of rejuvenating a nucleus that no other cell has."

30% is pretty high. Is that in frogs?

That's in frogs. But in mammals, assuming you're simply trying to derive one kind of cell from another—not trying to do an implantation—I would guess the efficiency is not that different.

So you think there's more at work in the egg than the four factors that Yamanaka described?

I don't quite know whether the egg makes use of those factors or not. People will soon find out. But it's very unlikely that eggs use just those four gene products.

If not, then why are they capable, albeit inefficiently, of converting cells back to a stem cell state?

Some people think that perhaps the fibroblasts go through a particular phase of the cell cycle in which they happen to be receptive to the four Yamanaka factors. Others, including Yamanaka himself, think that maybe the four factors have to arrive in the cell at an exactly precise ratio. And when you transfect, you rarely achieve that.

We've been doing some work describing the histone states of genes during reprogramming by nuclear transfer. It might be that by altering the histone state of genes that are the targets of the Yamanaka factors, we might make those genes more receptive and thus increase reprogramming efficiency. JCB

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4. Takahashi, K., and S. Yamanaka. 2006. *Cell.* 126:663–676.