

More lessons from Dolly the sheep—is a clone really born at age zero?

February 20 2017, by José Cibelli



More Dollies, cloned from the same cell line. Credit: Kevin Sinclair, University of Nottingham, CC BY-ND

In 1997 [Dolly the sheep was introduced](#) to the world by biologists Keith Campbell, Ian Wilmut and colleagues. Not just any lamb, Dolly was a clone. Rather than being made from a sperm and an egg, she originated from a mammary gland cell of another, no-longer-living, six-year-old Fynn Dorset ewe.

With her birth, a scientific and societal revolution was also born.

Some prominent scientists [raised doubts](#); it was too good to be true. But more animals were cloned: first the [laboratory mouse](#), then [cows](#), [goats](#), [pigs](#), [horses](#), even [dogs](#), [ferrets](#) and [camels](#). By early 2000, the issue was settled: Dolly was real and cloning adults was possible.

The implications of cloning animals in our society were self-evident from the start. Our advancing ability to reprogram adult, already specialized [cells](#) and start them over as something new may one day be the key to creating cells and organs that match the immune system of each individual patient in need of replacements.

But what somehow got lost was the fact that a clone was born – at day zero – created from the cell of another animal that was six years old. Researchers have spent the past 20 years trying to untangle the mysteries of how clones age. How old, biologically, are these animals born from other adult animals' cells?



Credit: Mikhail Nilov from Pexels

Decades of cloning research

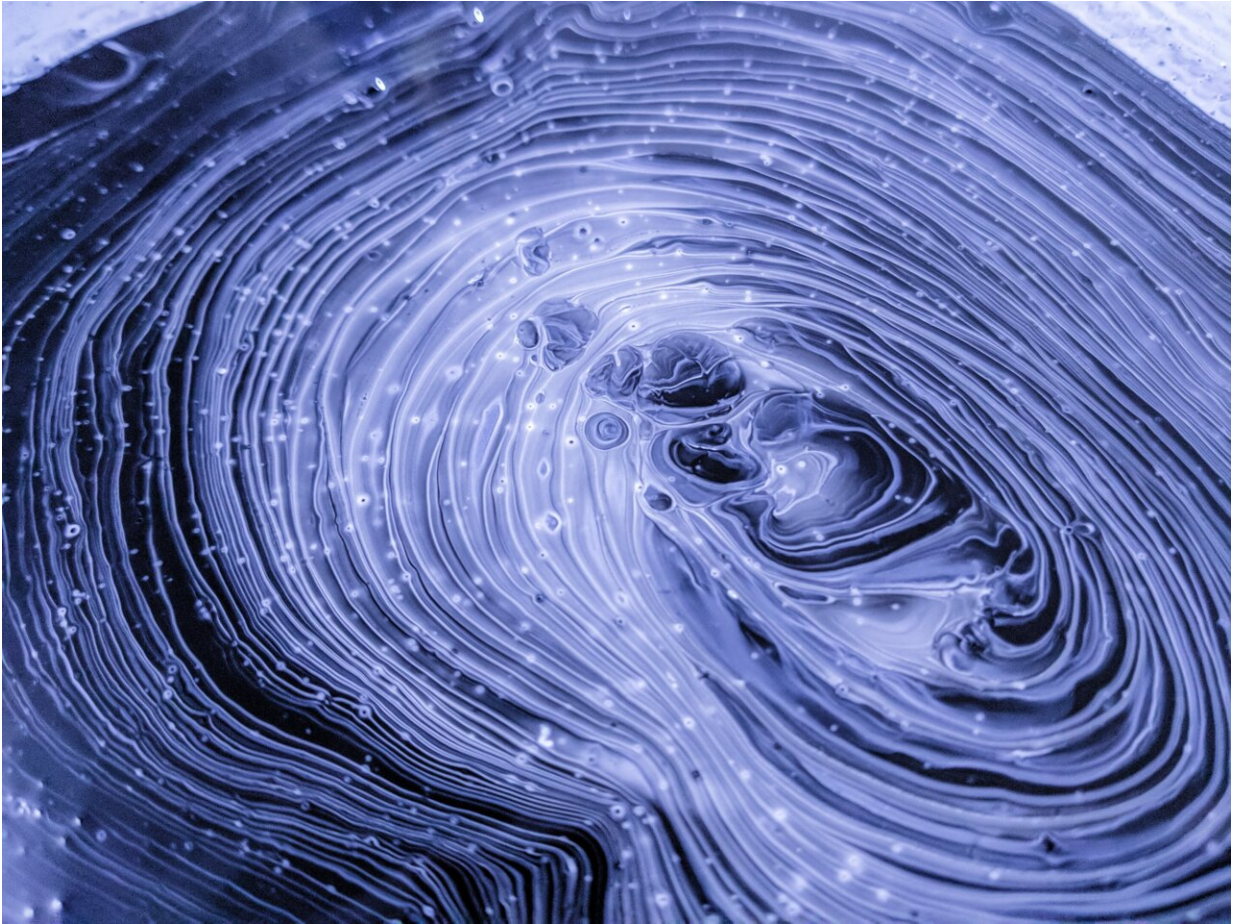
Dolly became an international celebrity, but she was not the first vertebrate to be cloned from a cell taken from the body of another animal. In 1962, developmental biologist [John Gurdon cloned the first adult animal](#) by taking a cell from the intestine of one frog and injecting it into an egg of another. Gurdon's work did not go unnoticed – he went on to share the [2012 Nobel Prize](#) in Physiology or Medicine. But it was Dolly who had captured our imagination. Was it because she was a warm-blooded animal, a mammal, much closer to human? If you could do it in a sheep, you could do it on us!

Dolly, along with Gurdon's frogs from 35 years earlier and all the other experiments in between, redirected our scientific studies. It was amazing to see a differentiated cell – an [adult cell](#) specialized to do its particular job – transform into an embryonic one that could go on to give rise to all the other cells of a normal body. We researchers wondered if we could go further: Could we in the lab make an adult cell once again undifferentiated, without needing to make a cloned embryo?

A decade after Dolly was announced, stem cell researcher [Shinya Yamanaka's team](#) did just that. He went on to be the Nobel corecipient with Gurdon for showing that mature cells could be [reprogrammed to become pluripotent](#): able to develop into any specialized adult cell.

Now we have the possibility of making individualized replacement cells – potentially any kind – to replace tissue damaged due to injury, genetic disorders and degeneration. Not only cells; we may soon be able to have [our own organs grown in a nonhuman host](#), ready to be transplanted when needed.

If Dolly was responsible for unleashing the events that culminate with new methods of making fully compatible cells and organs, then her legacy would be to improve the health of practically all human beings on this planet. And yet, I am convinced that there are even better things to come.



Credit: CC0 Public Domain

Dolly's secrets still unfolding

In the winter of 2013, I found myself driving on the wrong side of the road through the Nottingham countryside. In contrast to the luscious landscape, I was in a state gloom; I was on my way to see Keith Campbell's family after his sudden death a few weeks earlier. Keith was a smart, fun, loving friend who, along with Ian Wilmut and [colleagues at the Roslin Institute](#), had brought us Dolly 15 years earlier. We had met at a conference in the early 1990s, when we were both budding scientists

playing around with cloning, Keith with sheep, me with cows. An extrovert by nature, he quickly dazzled me with his wit, self-deprecating humor and nonstop chat, all delivered in a thick West Midlands accent. Our friendship that began then continued until his death.

When I knocked at the door of his quaint farmhouse, my plan was to stay just a few minutes, pay my respects to his wife and leave. Five hours and several Guinnesses later, I left feeling grateful. Keith could do that to you, but this time it wasn't him, it was his latest work speaking for him. That's because his wife very generously told me the project Keith was working on at the time of his death. I couldn't hide my excitement: Could it be possible that after 20 years, the most striking aspect of Dolly's legacy was not yet revealed?

See, when Dolly was cloned, she was created using a cell from a six-year-old sheep. And [she died at age six and a half](#), a premature death for a breed that lives an average of nine years or more. People assumed that an offspring cloned from an adult was starting at an age disadvantage; rather than truly being a "newborn," it seemed like a clone's internal age would be more advanced than the length of its own life would suggest. Thus the notion that clones' biological age and their chronological one were out of sync, and that "cloned animals will die young."

Some of us were convinced that if the cloning procedure was done properly, the biological clock should be reset – a newborn clone would truly start at zero. We worked very hard to prove our point. We were not convinced by a single DNA analysis done in Dolly showing slightly shorter [telomeres](#) – the repetitive DNA sequences at the end of chromosomes that "count" how many times a cell divides. We presented strong scientific evidence showing that cloned cows had all the [same molecular signs of aging](#) as a nonclone, predicting a normal lifespan. Others [showed the same in cloned mice](#). But we couldn't ignore reports from colleagues interpreting [biological signs in cloned animals](#) that they

attributed to [incomplete resetting of the biological clock](#). So the jury was out.

Aging studies are very hard to do because there are only two data points that really count: date of birth and date of death. If you want to know the lifespan of an individual you have to wait until its natural death. Little did I know, that is what Keith was doing back in 2012.



Four 8-year-old Finn-Dorset clones born in July 2007 and derived from the mammary gland cell line that gave rise to Dolly. Credit: K. D. Sinclair, S. A. Corr, C. G. Gutierrez, P. A. Fisher, J.-H. Lee et al. doi:10.1038/ncomms12359, CC BY

That Saturday afternoon I spent in Keith's house in Nottingham, I saw a photo of the animals in Keith's latest study: several cloned Dobbies, all much older than Dolly at the time she had died, and they looked terrific.

I was in awe.

The data were confidential, so I had to remain silent until late last year when [the work was posthumously published](#). Keith's coauthors humbly said: "For those clones that survive beyond the perinatal period [...] the emerging consensus, supported by the current data, is that they are healthy and seem to age normally."

These findings became even more relevant when last December researchers at the [Scripps Research Institute](#) found that induced [pluripotent stem cells](#) reprogrammed using the "Yamanaka factors" [retain the aging epigenetic signature of the donor individual](#). In other words, using these four genes to attempt to reprogram the cells does not seem to reset the [biological clock](#).

The new Dollys are now telling us that if we take a cell from an animal of any age, and we introduce its nucleus into a nonfertilized mature egg, we can have an individual born with its lifespan fully restored. They confirmed that all signs of biological and chronological age matched between cloned and noncloned sheep.

There seems to be a natural built-in mechanism in the eggs that can rejuvenate a cell. We don't know what it is yet, but it is there. Our group as well as others are hard at work, and as soon as someone finds it, the most astonishing legacy of Dolly will be realized.

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