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Sir Ian Wilmut 1944–2023

By Alan Trounson & Jose Cibelli

Ian Wilmut passed away on 10 September 2023 in his beloved Scotland. Ian was a prince of a person, gentle, friendly and forever an innovative scientist. Many years before Dolly – the cloned sheep that would bring him worldwide fame – Ian began his scientific career working on cryopreservation methods for animal spermatozoa and embryos. His 1971 PhD thesis, under the supervision of Ernest John Christopher Polge at the University of Cambridge's Agricultural Research Council (ARC), described a method to freeze and thaw boar spermatozoa. Assisted reproductive techniques using cryopreserved cells and embryos were a subject of great interest at the time for applications in breeding livestock. Ian became interested in applying the latest technologies to improve selective breeding in sheep and cattle, and in 1973, while he was in Polge's laboratory and one of us (A.T.) was working at the ARC, he produced Frostie, the first calf born from a frozen and thawed embryo[1]. This was an era of intense creativity in mammalian embryology at the ARC and worldwide. David Whittingham at Cambridge University had just shown that cryopreserved mouse embryos could give rise to healthy pups[2]. In 1981, two groups described the derivation of mouse embryonic stem cells[3,4]. At the ARC, Steen Willadsen produced the first chimeric sheep (a set of sheep–goat chimeras)[5], and embryo transfer was achieved in sheep[6], horse[7] and cattle[8]. By 1986, Willadsen reported the first cloned sheep from nuclei of blastomeres from 8- and 16-cell embryos[9]. Insights from animal embryology were also being applied to humans to treat infertility, with the birth in 1978 of the first baby through in vitro fertilization and, five years later, the demonstration (in the laboratory of A.T.) that human cryopreserved embryos could establish a pregnancy[10].

The stage was set for Ian to work on translating these early findings to domestic animals for agricultural and biomedical applications. A highly sought-after goal at the time was to create transgenic animals capable of producing human recombinant proteins at an affordable cost. After Ian moved to Edinburgh to what is now known as the Roslin Institute, he and his team pursued a two-pronged approach: generating sheep embryonic stem cells to make germline chimeric animals and developing direct pronuclear microinjection into embryos. The interest was driven by the biopharmaceutical company Pharming, which sought to manufacture large quantities of the human enzyme α1-antitrypsin in animals for the treatment of the lung diseases cystic fibrosis and emphysema. Using a technique for injecting human DNA into the pronuclei of single-celled embryos, Ian and his team produced Tracy, a genetically engineered sheep that secreted the human enzyme in her milk[11].

Sir Ian Wilmut.

Among other things, his group became proficient at culturing embryo-derived cells with normal karyotypes[12]. After the arrival of Keith Campbell, a frog nuclear-transfer researcher who was aware of the importance of coordinating the cell cycle of the donor nucleus with that of the recipient oocyte, they first introduced Megan and Morag, two sheep derived from embryonic cells that had been cultured in vitro and rendered quiescent by serum starvation[13]. Only a year later, in 1997, they reported Dolly, cloned from a cell taken from an adult sheep[14] – perhaps the most astonishing development in embryology of all time. Ian told one of us (A.T.) about Dolly during a hike in the hills above Edinburgh. I could not believe what he was saying because the great scientists working on amphibia and mice had, after exhaustive experimentation, dismissed the possibility that completely competent offspring could be cloned from differentiated adult cells. I remember saying to Ian that we would need to change the lecture notes on nuclear commitment in development – hardly an appropriate response.

Dolly arose from a negative control group in an experiment focused on nuclear transfer from embryonic and fetal cells. It was a stunning development in biology because the general view among scientists was that cell nuclei become irreversibly committed in early embryonic development and cannot be reprogrammed by insertion into the oocyte environment. Ian went on to combine cloning with genetic engineering. In late 1997, his team reported the sheep Polly and Molly, produced by nuclear transfer of fetal fibroblasts containing the human gene for factor IX, with the aim of producing this blood clotting factor for patients with hemophilia. Ian later became an advocate for therapeutic cloning – the use of nuclear transfer to create embryonic stem cells for regenerative purposes in patients with severe diseases[15].

Humbleness and stoicism were hallmarks of Ian's personality. After the publication of Dolly, he and his team had to endure criticism from all directions. Not once was he rattled by it. His responses were backed by data, and if the discussion surpassed his expertise and training, he would say so. The sharpest criticism came from American scientists in January of 1998. Almost a year had passed since Dolly's announcement and no laboratory had replicated the experiment when Sgaramella and Zinder published a letter[16] in *Science* questioning the validity of the original report. Ian knew of confirmatory work from our[17] and another[18] laboratory that was close to publication, which he could have mentioned in his response. He chose not to; instead, he offered these assertive and gracious words: "We were always aware that there would be some scepticism about our results and have been greatly encouraged by the positive reaction of the scientific community. We would like to think that this reflects the integrity with which we are accredited by our scientific peers." Two years later, in the spring of 2000, at a cloning meeting organized at the Banbury Center by Cold Spring Harbor Laboratory, Ian unpretentiously shared laughs with Norton Zinder.

By then, many of his peers had repeated his work in mice, cows, goats and pigs.

Ian was a leader in advocating the ethical use of nuclear transfer in medicine and research. Early animal cloning studies had noted developmental abnormalities, bringing safety concerns to the fore[19]. Ian opposed the use of cloning in human reproductive embryology because of the genetic risks that could be inherited and the availability of other treatment options for people with infertility. This view was enshrined in formal guidelines for scientists issued by the International Society for Stem Cell Research. To our knowledge, reproductive cloning of humans has never been attempted, despite the claims of a few rogue individuals. We think Ian's leadership had much to do with the blanket ban that is strongly endorsed by all scientists worldwide, even though human nuclear transfer has been used to generate stem cell lines[20] and there is no technical reason that reproductive cloning could not be done.

Today, nuclear transfer has an enduring role in animals. Work in a large array of animals has shown its utility in breeding, in the rescue of animal populations after calamities or insufficient breeding, and in the recovery of endangered and extinct species, such as the endangered black-footed ferret and extinct gastric-brooding frogs *Rheobatrachus silus* and *R. vitellinus*, provided that a closely related species is available as a host oocyte and maternal embryonic incubator.

Ian will be fondly remembered by all who had the privilege of his company. He was always interested in other people and their work; he was humorous and enjoyed company. He hosted us many times at his home; he was content and eager to know what we were up to with our work and private lives. It was all about us, not him, until the twilight of his life. He was respectful and led by example at work, in conferences, workshops and in his personal life. There was everything to like about Ian. His family and friends will miss him, and the world will be poorer by his passing.

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