Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: V: Dolly the sheep - the first cloned mammal and a public icon for regenerative medicine

1. Summary of the impact (indicative maximum 100 words)

Impact: Public engagement and education, influence on public ethical and scientific policy.

Significance: The first demonstration of cloning from an adult mammalian somatic cell has stimulated rolling religious, ethical, cultural, political and scientific debates. Dolly has become a scientific icon entering the public and educational lexicons in addition to scientific ones.

Beneficiaries: Human society, culture, education.

Attribution: Wilmut and colleagues (Roslin Institute, UoE), undertook somatic cell nuclear transfer and used it to perform the first successful cloning of an adult mammal.

Reach: Worldwide: Dolly became a scientific icon that is recognisable all around the world, representing a major public engagement with bioscience. For example; cloning principles are part of high school education including the International Baccalaureate (implemented in >3600 schools on five continents).

2. Underpinning research (indicative maximum 500 words)

Professor Sir Ian Wilmut (Chair of Reproductive Biology, UoE, 1973–2011; now Emeritus) led the team that used somatic cell nuclear transfer (SCNT) to create Dolly. This scientific breakthrough is widely recognised as the key stepping stone between the earlier amphibian-based work of Gurdon and the reprogramming of adult human somatic cells to a stem cell state (induced pluripotent stem cells) by Yamanaka.

Wilmut, with colleagues from the Roslin Institute (now UoE), focused their scientific efforts on the manipulation of eggs (female reproductive cells), oocytes (egg precursor cells) and stem cells (cells that can divide and self-renew, but also differentiate into diverse specialised cell types). They were particularly interested in utilising SCNT to produce viable embryos. This technique involves transfer of the nucleus from a somatic cell (any cell that is not a reproductive or stem cell) into an oocyte or egg deprived of its own nucleus (cytoplast).

In 1994, Wilmut and colleagues discovered that the development of embryos reconstructed by nuclear transfer is related to interactions between the donor nucleus and the recipient cytoplasm at the time of fusion and during the first cell cycle after reconstruction [3.1]. This led to the proposal of two distinct protocols for embryo reconstruction by nuclear transfer when using MII oocytes (oocytes at the metaphase II stage of cell division) as cytoplasts: (i) transfer of nuclei in G1 phase of the cell cycle into MII cytoplasts containing a high activity of the so-called maturation-promoting factor (MPF), and (ii) transfer of nuclei in G1, S or G2 phase into enucleated oocytes after the disappearance of MPF activity (in the so-called “universal recipient” stage). The group also showed that it was possible to use microtubule inhibitors such as nocodazole to hold cells in mitosis before releasing them and using them as nuclear donors as they passed through G1 phase [3.2, 3.3]. Unfortunately, although this synchronisation method worked in mice, it proved to be unreliable in embryos of livestock species. Consequently, Wilmut and colleagues developed a different approach for the synchronisation of donor nuclei. The approach was based on serum-starvation of donor cells, which forced them to arrest in the G0/G1 phase of the cell cycle (the so-called state of quiescence). This enabled the successful cloning of sheep from cultured cells derived from sheep

embryos. This study was published in early 1996 [3.4]. The same procedure allowed the group to clone a sheep using a nucleus derived from an adult mammary gland cell. Dolly — the first cloned adult mammal — was born on July 5, 1996, providing the first evidence that adult specialised cells are capable of driving the development of a complete and fertile animal. This first successful cloning of an adult mammal was reported in Nature in 1997 [3.5] and met with huge and sustained public and media interest (Fig. 1).

Fig. 1

3. References to the research (indicative maximum of six references)

3.1 Campbell K, Loi P, Cappai P, Wilmut I. Improved development to blastocyst of ovine nuclear transfer embryos reconstructed during the presumptive S-phase of enucleated activated oocytes. Biol Reprod. 1994;50:1385–93. DOI: 10.1095/biolreprod50.6.1385.

3.2 Otaegui P, O'Neill G, Campbell K, Wilmut I. Transfer of nuclei from 8-cell stage mouse embryos following use of nocodazole to control the cell cycle. Mol Reprod Dev. 1994;39:147–52. DOI: 10.1002/mrd.1080390205.

3.3 Otaegui P, Waddington D, Wilmut I. Nuclear transfer of 4-cell mouse embryos: synchronisation with cytoplast partially overcomes nuclear donor cell-cycle effect. J Reprod Fertil Abstr Ser 13. 1994;Abstract 24.

3.4 Campbell K, McWhir J, Ritchie W, Wilmut I. Sheep cloned by nuclear transfer from a cultured cell line. Nature. 1996;380:64–6. DOI: 10.1038/380064a0.

3.5 Wilmut I, Schnieke A, McWhir J, Kind A, Campbell K. Viable offspring derived from fetal and adult mammalian cells. Nature. 1997;385:810–813. DOI: 10.1038/385810a0.

4. Details of the impact (indicative maximum 750 words)

Pathways to impact

Improvements made to SCNT and the successful cloning of Dolly the sheep challenged the dogma that the genetic material of specialised cells is no longer capable of driving the development of a complete animal. This momentous achievement opened new frontiers in science, technology and medicine. It also inspired heated debate on the essence of humanity among scientists, philosophers, religious leaders, politicians and the public. Dolly the sheep found her place among major scientific achievements and her legacy continues to have enormous impact. Wilmut has played a key role in the public engagement surrounding mammalian stem cell cloning, delivering 49 public lectures since 2008.

Impact on society, public scientific and ethical policy

The realisation that it is possible to clone adult mammals had profound implications for religious organisations and led to the introduction of new laws and ethical guidelines. Although many were instituted prior to 2008, the "legacy of Dolly" continues to impact on ethical debate in the religious, secular and legislative arenas. For example, the cloning of Dolly is specifically referred to in a recent church position statement: "A statement of the United States Conference of Catholic Bishops on embryonic stem cell research" published for the first time in June 2008 [5.1], and in numerous recently published books on ethics [5.2]. "Dolly" continues to inform governmental thinking and policy: for example, in 2008, the European Group on Ethics of Science and New Technologies (EGE), in response to a request from the European Commission, issued an opinion on the ethical implications of cloning animals for food supply [5.3]; and the Australian government requested a review of its Prohibition of Human Cloning for Reproduction and Research Involving Human Embryos Acts in December 2010 [5.4].

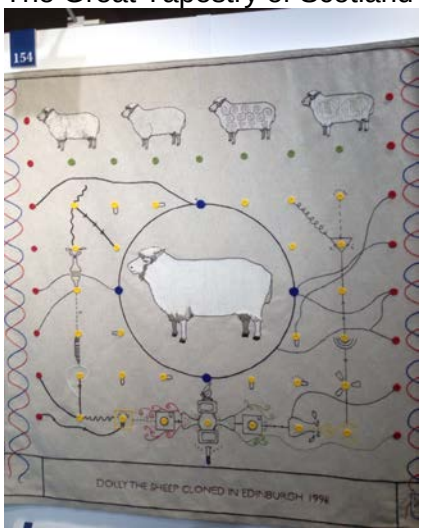
Impact on society, public engagement, arts and culture

The life and death of Dolly continues to have a significant impact on art and culture. For example, a

mask taken from Dolly the sheep was one of the highlights at the Scottish National Portrait Gallery at its reopening after major renovation in 2011 (11,186 visitors within the first four days after reopening alone) [5.5], and Krystelle Bamford, a winner of the 2010 New Writers Award, wrote a poem entitled "On the Death Mask of Dolly the Sheep" that was published in the November 2012 issue of the American Poetry Review, a major international poetry magazine based in the USA [5.6]. Dolly and the scientists who created her were also featured in the exhibition "Cells – the smallest of all portraits", an experimental learning project involving pupils from Scottish schools (October 29th 2012 – February 3rd 2013, Scottish National Portrait Gallery).

The manner in which Dolly as a scientific icon has caught the public imagination is unlike few scientific discoveries of the last decades. Starting with extensive broadsheet coverage, including the cover of Time magazine (Fig. 1 in section 2), the media interest in and reach of Dolly has demonstrated extraordinary breadth and durability. Since 2008, reference to Dolly and cloning have appeared in numerous media relevant to a wide range of age groups ranging from the "Itchy & Scratchy" cartoon and "The Simpsons Comic" to the recently completed "Great Tapestry of Scotland", in which a whole panel is devoted to Dolly to represent Scottish scientific discovery (Fig. 2).

Fig. 2
The Great Tapestry of Scotland



The Simpsons Comic

Impact on society, public engagement and education
Dolly herself has become a "scientific icon" of UK biomedical science and is displayed in the National Museum of Scotland in Edinburgh (1.9M visitors annually). The National Museum of Scotland website lists Dolly as a highlight, and states that "Dolly has been enormously popular, with visitors coming from all over the world to see her. She has even travelled to Hungary to open a new science museum in Budapest!" [5.7].

The principles of SCNT are now part of the science curriculum at high school level in the UK and other countries. Notably, they have been integrated into the International Baccalaureate (IB) Diploma curriculum [5.8], a two-year educational programme primarily aimed at students aged 16–19 that provides an internationally accepted qualification for entry into higher education, and is recognised by many universities worldwide. IB courses are available in 3628 schools in Europe, North America, South America, Asia and Africa [5.9].

Impact on society, public science policy
Dolly played a major role in clarifying the value of stem cell and regenerative medicine research to Government, contributing to the establishment of several high-profile initiatives including the UK Stem Cell Initiative chaired by Sir John Pattison. More recently, in autumn 2012, the Chancellor of the Exchequer identified Eight Great Technologies of strategic importance to the UK and announced an additional funding of £600M to help support their development. Regenerative

medicine is placed among these great technologies and the influence of Dolly the Sheep and Edinburgh's research was highlighted in a speech by the Minister for Universities and Science (the Rt Hon David Willetts MP) delivered on January 24, 2013 at the Policy Exchange [5.10].

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 A statement of the United States Conference of Catholic Bishops on embryonic stem cell research. USCCB Publishing, Washington, D.C., 2008. http://old.usccb.org/prolife/issues/bioethic/bishopsESCRstmt.pdf.

5.2 Examples of major books on ethics that specifically mention the cloning of Dolly the sheep *[available on request]*:

- Ravitsky V, Fiester A, Caplan A. The Penn Center Guide to Bioethics. Springer Publishing Company, New York, USA, 2009.
- Morrison E. Health Care Ethics: Critical Issues for the 21st Century, second edition. Jones and Bartlett Publishers, London, UK, 2008.

5.3 The European Group on Ethics in Science and New Technologies to the European Commission Opinion 23 - Ethical aspects of animal cloning for food supply, 2008. http://ec.europa.eu/bepa/european-group-ethics/docs/publications/opinion23_en.pdf.

5.4 Report of the Independent Review of the Prohibition of Human Cloning for Reproduction Act 2002 and Research Involving Human Embryos Act 2002 - A Report to the Parliament and the Council of Australian Governments, 2011. https://legislationreview.nhmrc.gov.au/files/legislation_review_reports.pdf.

5.5 Record number of visitors to Scottish National Portrait Gallery, STV news, 6 December 2011 by Clare Carswell. http://news.stv.tv/east-central/285503-scottish-national-portrait-gallery-announces-record-number-of-visitors/. *[Corroborates number of visitors to gallery.]*

5.6 Bamford K. On the Death Mask of Dolly the sheep. American Poetry Review. Nov/Dec 2012;41:46. *[Available on request.]*

5.7 National Museum of Scotland website. http://www.nms.ac.uk/our_collections/highlights/dolly_the_sheep.aspx.

5.8 Walpole B, Merson-Davis A, Dann L. Biology for the IB Diploma. Cambridge University Press 2011. *[Available on request. International Baccalaureate diploma programme textbook; Dolly mentioned on page 94].*

5.9 Statistics available from the website of the International Baccalaureate Organisation. http://www.ibo.org/facts/schoolstats/progcombinationsbyregion.cfm.

5.10 Policy: Investing in research,development and innovation; Speech: Eight Great Technologies, Minister: The Rt Hon David Willetts MP; Date: 24 Jan 2013; Place: Policy Exchange; Transcript: https://www.gov.uk/government/speeches/eight-great-technologies.