CSIRO PUBLISHING

Reproduction, Fertility and Development, 2015, **27**, xxvi–xxviii
http://dx.doi.org/10.1071/RDv27n1_PA2

Recipient of the 2015 IETS Pioneer Award: Keith Henry Stockman Campbell, PhD

Dr Keith Henry Stockman Campbell was born in Birmingham, England, to an English mother and Scottish father. He started his education in Perth, Scotland, but when he was 8 years old, his family returned to Birmingham. He was educated at King Edward VI Grammar School for boys and then trained and became qualified as a medical laboratory technologist specialising in medical microbiology at Selly Oak Hospital. At age 21, Keith attended Queen Elizabeth College, London, where he obtained a BSc in microbiology in 1983. During these studies, he became interested in the cell cycle and cellular growth. Following brief positions, first as chief medical laboratory technologist in Southern Yemen and then on a program to eradicate Dutch elm disease in parts of Southern England, he joined the cytogenetics group of Dr Bishun at the Marie Curie Institute. At the Curie Foundation, Keith's interests in the regulation of cellular growth, particularly differentiation, increased. In 1983, he was awarded the Marie Curie Research Scholarship and moved to the University of Sussex as a postgraduate student where he studied the cytoplasmic control of nuclear behaviour during the development of amphibian eggs, early embryos, and during cell growth and division in yeast. Keith was particularly interested in the ubiquitous nature of such cytoplasmic factors in eukaryotic cell types. He was awarded a PhD for his thesis titled 'Aspects of cell cycle control in Yeast and Xenopus'. After these studies Keith returned to Scotland, not only to pursue his career but also because of his love of the outdoors and his keen interests in hill walking and mountain biking. Following two postdoctoral fellowships, Keith joined the Roslin Institute in 1991 to study animal cloning by nuclear transplantation. Keith's interests in cloning mammals were inspired by work done by Karl Illmensee and John Gurdon.

At Roslin, Keith initiated and conducted cloning experiments in collaboration with Ian Wilmut. Keith applied the knowledge gained from his studies in cancer and amphibian embryos and his interests in cell specialisation to studies on nuclear equivalence in mammals. At that time it was known that the majority of cells within an adult contain an intact genome; however, many scientists were skeptical that the nuclei of such cells could be reprogrammed to become totipotent. Stubbornly, Keith always believed that most differentiated cells maintained equivalency, and in 1995 his studies in collaboration with William Ritchie led to the birth of Megan and Morag, two Welsh Mountain lambs. These were the first mammals to be cloned from cultured differentiated cells. In 1996, these experiments were extended, resulting in the birth of Dolly, a Finn Dorset sheep that became the first mammal to be cloned from an adult-derived somatic cell. Keith utilised his crucial idea of coordinating the stages of the cell cycle of the donor somatic cells with the recipient eggs while using diploid quiescent or 'G0' arrested somatic cells as nuclear donors. With this notion he shocked the world by successfully cloning a sheep from adult mammary cells.

In 1997, William Ritchie and Keith, in collaboration with PPL (Pharmaceutical Proteins Limited), used nuclear transfer techniques to produce two sheep named Polly and Molly, derived from genetically altered skin cells containing a human gene coding for human blood clotting factor IX. In 2000, after joining PPL Ltd, Keith and his PPL team (based in North America) were successful in producing the world's first piglets by somatic cell nuclear transfer (SCNT). Furthermore, the PPL teams based in Roslin, Scotland, and Blacksburg, Virginia, USA, used the techniques to produce the first gene targeted domestic animals as well as a wide range of animals producing human therapeutic proteins in their milk.

From November 1999, Keith Campbell held the post of professor of animal development, Division of Animal Physiology, School of Biosciences, at the University of Nottingham where he continued to study embryo growth and differentiation. His research into the basic mechanisms underlying early development and cellular differentiation provided knowledge on epigenetic programming of nuclear and chromatin structures involved in controlling and maintaining cellular differentiation. Keith believed that understanding and improving the cloning process has many applications in basic and applied research for both human medicine and agriculture. However, the major objectives of Keith's studies were to understand the epigenetic control and to reprogram differentiated cells to become stem cells, whilst avoiding the requirement for embryo production. This would not only allow development of cell based models for many studies in aging and age-related diseases, but also aid in

the development of novel therapies for both human and veterinary applications.

Keith supported the use of SCNT for the production of personalized stem cell therapies, the study of human diseases, and the use of 'cybrid' embryo production to overcome the lack of human eggs available for research. Stem cells can be isolated from embryonic, fetal, and adult derived material and more recently by overexpression of certain genes for the production of 'induced pluripotent cells'. Keith's experiments demonstrated that all cells had pluripotent potential and thus opened the door to the new field of cellular reprogramming. Keith believed all potential stem cell populations should be used for both basic and applied research, which may provide scientific knowledge and lead to the development of cell-based therapies.

In 2008, he received the Shaw Prize for Medicine and Life Sciences jointly with Ian Wilmut and Shinya Yamanaka. Keith lectured regularly to both scientific and lay audiences and liaised with the press on current advances in biotechnology, giving regular interviews to the newspapers, radio, and TV. He believed that public understanding of science is crucial for continued research and introduction of the benefits produced in many areas.

Dr Keith H. S. Campbell is recognised as one of the fathers of Dolly, the first animal to develop after nuclear transfer from an adult cell, and was a pioneer in the science of cloning. One of Dr Campbell's distinguishing characteristics was his unrelenting pursuit of new knowledge. He dedicated his life to the improvement and mainstreaming of embryo related technologies into livestock production around the world. He performed all these contributions while keeping his friends and colleagues laughing and was quick to remind us that our work should be meaningful and fun. Therefore, in recognition of the significant contributions he made to the international scientific, academic, medical, veterinary, embryo transfer, and biotechnology communities, the IETS is proud to award Dr Keith H. S. Campbell with the 2015 International Embryo Transfer Society Pioneer Award.

References

Alberio, R., Johnson, A. D., Stick, R., and Campbell, K. H. (2005). Differential nuclear remodeling of mammalian somatic cells by Xenopus laevis oocyte and egg cytoplasm. *Exp. Cell Res.* **307**(1), 131–141. doi:10.1016/J.YEXCR.2005.02.028

Amarnath, D., Wakayama, S., Zhu, J., Moawad, A. R., Wakayama, T., and Campbell, K. H. (2011*a*). The novel use of modified pig zygotic medium for the efficient culture of the preimplantation mouse embryos. *Theriogenology* **76**(9), 1639–1646. doi:10.1016/J.THERIOGENOLOGY.2011.06.028

Amarnath, D., Choi, I., Moawad, A. R., Wakayama, T., and Campbell, K. H. (2011*b*). Nuclear-cytoplasmic incompatibility and inefficient development of pig-mouse cytoplasmic hybrid embryos. *Reproduction* **142**(2), 295–307. doi:10.1530/REP-11-0044

Bian, Y., Alberio, R., Allegrucci, C., Campbell, K. H., and Johnson, A. D. (2009). Epigenetic marks in somatic chromatin are remodelled to resemble pluripotent nuclei by amphibian oocyte extracts. *Epigenetics* **4**(3), 194–202. doi:10.4161/EPI.4.3.8787

Bowles, E. J., Campbell, K. H., and St John, J. C. (2007). Nuclear transfer: preservation of a nuclear genome at the expense of its associated mtDNA genome(s). *Curr. Top. Dev. Biol.* **77**, 251–290. doi:10.1016/S0070-2153(06)77010-7

Campbell, K. H., Ritchie, W. A., and Wilmut, I. (1993). Nuclear-cytoplasmic interactions during the first cell cycle of nuclear transfer reconstructed bovine embryos: implications for deoxyribonucleic acid replication and development. *Biol. Reprod.* **49**(5), 933–942. doi:10.1095/BIOLREPROD49.5.933

Campbell, K. H., Loi, P., Cappai, P., and Wilmut, I. (1994). Improved development to blastocyst of ovine nuclear transfer embryos reconstructed during the presumptive S-phase of enucleated activated oocytes. *Biol. Reprod.* **50**(6), 1385–1393. doi:10.1095/BIOLREPROD50.6.1385

Campbell, K. H., McWhir, J., Ritchie, W. A., and Wilmut, I. (1996*a*). Sheep cloned by nuclear transfer from a cultured cell line. *Nature* **380**(6569), 64–66. doi:10.1038/380064A0

Campbell, K. H., Loi, P., Otaegui, P. J., and Wilmut, I. (1996*b*). Cell cycle co-ordination in embryo cloning by nuclear transfer. *Rev. Reprod.* **1**(1), 40–46. doi:10.1530/ROR.0.0010040

Choi, I., Lee, J. H., Fisher, P., and Campbell, K. H. (2010). Caffeine treatment of ovine cytoplasts regulates gene expression and foetal development of embryos produced by somatic cell nuclear transfer. *Mol. Reprod. Dev.* **77**(10), 876–887. doi:10.1002/MRD.21230

Choi, I., Zhu, J., and Campbell, K. H. (2013). The combined treatment of calcium ionophore with strontium improves the quality of ovine SCNT embryo development. *Zygote* **21**(2), 139–150. doi:10.1017/S0967199412000470

Fouladi Nashta, A. A., Waddington, D., and Campbell, K. H. (1998). Maintenance of bovine oocytes in meiotic arrest and subsequent development *In vitro*: A comparative evaluation of antral follicle culture with other methods. *Biol. Reprod.* **59**(2), 255–262. doi:10.1095/BIOLREPROD59.2.255

Fouladi-Nashta, A. A., Alberio, R., Kafi, M., Nicholas, B., Campbell, K. H., and Webb, R. (2005). Differential staining combined with TUNEL labeling to detect apoptosis in preimplantation bovine embryos. *Reprod. Biomed. Online* **10**(4), 497–502. doi:10.1016/S1472-6483(10)60827-9

Iwasaki, S., Campbell, K. H., Galli, C., and Akiyama, K. (2000). Production of live calves derived from embryonic stem-like cells aggregated with tetraploid embryos. *Biol. Reprod.* **62**(2), 470–475. doi:10.1095/BIOLREPROD62.2.470

Kill, I. R., Bridger, J. M., Campbell, K. H., Maldonado-Codina, G., and Hutchison, C. J. (1991). The timing of the formation and usage of replicase clusters in S-phase nuclei of human diploid fibroblasts. *J. Cell Sci.* **100**(Pt 4), 869–876.

Lee, J. H., and Campbell, K. H. (2006). Effects of enucleation and caffeine on maturation-promoting factor (MPF) and mitogen-activated protein kinase (MAPK) activities in ovine oocytes used as recipient cytoplasts for nuclear transfer. *Biol. Reprod.* **74**(4), 691–698. doi:10.1095/BIOLREPROD.105.043885

Lee, J. H., and Campbell, K. H. (2008). Caffeine treatment prevents age-related changes in ovine oocytes and increases cell numbers in blastocysts produced by somatic cell nuclear transfer. *Cloning Stem Cells* **10**(3), 381–390. doi:10.1089/CLO.2007.0091

Lee, J. H., Peters, A., Fisher, P., Bowles, E. J., St John, J. C., and Campbell, K. H. (2010). Generation of mtDNA homoplasmic cloned lambs. *Cell. Reprogram.* **12**(3), 347–355. doi:10.1089/CELL.2009.0096

Maalouf, W. E., Alberio, R., and Campbell, K. H. (2008). Differential acetylation of histone H4 lysine during development of *in vitro* fertilized, cloned and parthenogenetically activated bovine embryos. *Epigenetics* **3**(4), 199–209. doi:10.4161/EPI.3.4.6497

Maalouf, W. E., Lee, J. H., and Campbell, K. H. (2009). Effects of caffeine, cumulus cell removal and aging on polyspermy and embryo development on *in vitro* matured and fertilized ovine oocytes. *Theriogenology* **71**(7), 1083–1092. doi:10.1016/J.THERIOGENOLOGY.2008.12.001

Meier, J., Campbell, K. H., Ford, C. C., Stick, R., and Hutchison, C. J. (1991). The role of lamin LIII in nuclear assembly and DNA replication, in cell-free extracts of Xenopus eggs. *J. Cell Sci.* **98**(Pt 3), 271–279.

Moawad, A. R., Fisher, P., Zhu, J., Choi, I., Polgar, Z., Dinnyes, A., and Campbell, K. H. (2012). *In vitro* fertilization of ovine oocytes vitrified by solid surface vitrification at germinal vesicle stage. *Cryobiology* **65**(2), 139–144. doi:10.1016/J.CRYOBIOL.2012.04.008

Moawad, A. R., Zhu, J., Choi, I., Amarnath, D., and Campbell, K. H. (2013*a*). Effect of Cytochalasin B. pretreatment on developmental potential of ovine oocytes vitrified at the germinal vesicle stage. *Cryo Letters* **34**(6), 634–644.

Moawad, A. R., Zhu, J., Choi, I., Amarnath, D., Chen, W., and Campbell, K. H. (2013*b*). Production of good-quality blastocyst embryos following IVF of ovine oocytes vitrified at the germinal vesicle stage using a cryoloop. *Reprod. Fertil. Dev.* **25**(8), 1204–1215. doi:10.1071/RD12215

Otaegui, P. J., O'Neill, G. T., Campbell, K. H., and Wilmut, I. (1994). Transfer of nuclei from 8-cell stage mouse embryos following use of nocodazole to control the cell cycle. *Mol. Reprod. Dev.* **39**(2), 147–152. doi:10.1002/MRD.1080390205

Polejaeva, I. A., Chen, S. H., Vaught, T. D., Page, R. L., Mullins, J., Ball, S., Dai, Y., Boone, J., Walker, S., Ayares, D. L., Colman, A., and Campbell, K. H. (2000). Cloned pigs produced by nuclear transfer from adult somatic cells. *Nature* **407**(6800), 86–90. doi:10.1038/35024082

Rathbone, A. J., Fisher, P. A., Lee, J. H., Craigon, J., and Campbell, K. H. (2010). Reprogramming of ovine somatic cells with Xenopus laevis oocyte extract prior to SCNT improves live birth rate. *Cell. Reprogram.* **12**(5), 609–616. doi:10.1089/CELL.2010.0015

Rathbone, A. J., Liddell, S., and Campbell, K. H. (2013). Proteomic analysis of early reprogramming events in murine somatic cells incubated with Xenopus laevis oocyte extracts demonstrates network associations with induced pluripotency markers. *Cell. Reprogram.* **15**(4), 269–280.

Wilmut, I., Schnieke, A. E., McWhir, J., Kind, A. J., and Campbell, K. H. (1997). Viable offspring derived from fetal and adult mammalian cells. *Nature* **385**(6619), 810–813. doi:10.1038/385810A0

Ye, J., Campbell, K. H., Craigon, J., and Luck, M. R. (2005). Dynamic changes in meiotic progression and improvement of developmental competence of pig oocytes *in vitro* by follicle-stimulating hormone and cycloheximide. *Biol. Reprod.* **72**(2), 399–406. doi:10.1095/BIOLREPROD.104.034553

Ye, J., Coleman, J., Hunter, M. G., Craigon, J., Campbell, K. H., and Luck, M. R. (2007). Physiological temperature variants and culture media modify meiotic progression and developmental potential of pig oocytes *in vitro*. *Reproduction* **133**(5), 877–886. doi:10.1530/REP-06-0318