

Somatic Cell Nuclear Transfer in Mammals (1938-2013) ^[1]

By: Bartlett, Zane Keywords: Dolly the sheep ^[2] Karl Illmensee ^[3] New York Stem Cell Foundation ^[4]

In the second half of the twentieth century, scientists learned how to clone some species of mammals. Scientists have applied [somatic cell nuclear transfer](#) ^[5] to clone human and mammalian embryos as a means to produce [stem cells](#) ^[6] for laboratory and medical use. Somatic cell nuclear transfer (SCNT) is a technology applied in [cloning](#) ^[7], stem cell research, and [regenerative medicine](#) ^[8]. Somatic cells are cells that have gone through the [differentiation](#) ^[9] process and are not germ cells. Somatic cells donate their nuclei, which scientists transplant into eggs after removing their nucleuses (enucleated eggs). Therefore, in SCNT, scientists replace the [nucleus](#) ^[10] in an [egg](#) ^[11] cell with the [nucleus](#) ^[10] from a [somatic cell](#) ^[12].

Although Karl Illmensee first cloned a [mammal](#) ^[13] in 1981, other scientists had theorized and developed the techniques needed for SCNT in the form of nuclear transfer. [Hans Spemann](#) ^[14], who taught zoology at the [University of Freiburg](#) ^[15] in Freiburg, Germany, theorized about SCNT in his 1938 book *Embryonic Development and Induction*. Spemann proposed to transplant a [nucleus](#) ^[10] from already differentiated cell from an embryo into an [egg](#) ^[11] after removing the [egg](#) ^[11]'s [nucleus](#) ^[10]. However, the technology required for this kind of experiment was not available to Spemann at that time, so he could not test his theory of nuclear transfer or SCNT. Robert King and Thomas Briggs developed the necessary protocol to conduct preliminary nuclear transfer at the [Institute for Cancer Research](#) ^[16] and [Lankenau Hospital Research Institute](#) ^[17] in Philadelphia, Pennsylvania, in 1952. The same nuclear transfer techniques serve as the basis for SCNT.

While researching how embryos differentiate in 1952, Briggs and King transplanted the [nucleus](#) ^[10] from an early embryonic [blastula](#) ^[18] cell of a *Rana pipiens* ^[19] [frog](#) ^[20] embryo to an unfertilized [egg](#) ^[11] after removing its [nucleus](#) ^[10]. To enucleate the eggs, Briggs and King used a small glass needle to puncture the cell membrane, enter the cytoplasm, and suck out the [nucleus](#) ^[10] of the [egg](#) ^[11] cell. Briggs and King then transplanted the donor [nucleus](#) ^[10] from a separate [blastula](#) ^[18] cell to replace the [nucleus](#) ^[10] that they removed from the [egg](#) ^[11] cell. Briggs and King observed that the embryo developed normally.

Researchers struggled to clone mammals using the same procedure that Briggs and King used on frogs. In 1975, Derek Bromhall in Oxford, UK, conducted experiments using [rabbit](#) ^[21] embryos and showed that, after a certain stage in development called the [morula stage](#) ^[22], embryos produced from nuclear transfer died. Bromhall hypothesized that they died as the result of complications from the punctures made in the cell membrane during the transfer.

Scientists performed nuclear transfer only on [amphibians](#) ^[23] until 1981, when Illmensee in Geneva, Switzerland, claimed to have cloned mice using nuclear transfer technique. His work resulted in the birth of three live mice. Illmensee's experiments came under scrutiny and an investigation occurred concerning the veracity of his claims. Although the investigators never found conclusive evidence against Illmensee, the investigation cast doubts as to whether or

not he had used nuclear transfer to clone the mice.

Scientists struggled to perform nuclear transfer on mammals larger than mice. [Steen Willadsen](#) [24] at the Institute of Animal Physiology in Babraham Institute in Babraham, United Kingdom, was the first to clone a [sheep](#) [25] embryo in 1984. Willadsen modified the technique of Briggs and King. After transferring the [nucleus](#) [10], Willadsen fused the embryo together using an electrofusion apparatus that has small electrodes that produce an electrical current. Willadsen coated the embryo with an agar jelly made from algae to reduce the damage caused by entry of the glass needle into the cell membrane. Once he had coated the embryos with agar jelly, Willadsen placed the embryos into the tied oviducts of a [sheep](#) [25], and he observed that the embryos were growing. From this experiment, Willadsen made [viable](#) [26] mammalian embryos using his modified techniques, but they didn't grow into adult organisms.

In 1996, Keith Campbell, Jim McWhir, William Ritchie, and [Ian Wilmut](#) [27] at the Roslin Institute in Edinburgh, UK, used nuclear transfer techniques to clone a [sheep](#) [25] that was born and grew into an adult. The team manipulated a stage in the cell cycle called quiescence, when the cell undergoes a period of supposed hibernation and ceases to develop. Campbell induced quiescence in the donor [blastocyst](#) [28] nuclei before transferring them to recipient [egg](#) [11] cells by depriving the cells of proteins called growth factors. The change in the state of the donor nuclei before entering the receiving [egg](#) [11] cells enabled embryos to develop to term in [surrogate](#) [29] ewes.

According to Wilmut, the next experiment applied the same procedure to the [nucleus](#) [10] of a fully differentiated adult cell as opposed to a [blastocyst](#) [28] cell. The Roslin team hypothesized that the nuclear transfer procedure started by Briggs and King could be applied to somatic cells, thus becoming [somatic cell](#) [12] nuclear transfer as opposed to just nuclear transfer. The Roslin Institute performed this step in 1997. The result of the experiment was Dolly the [sheep](#) [25].

Dolly was the first [mammal](#) [13] cloned from a fully differentiated adult cell. The main difference in the techniques producing Dolly was that the scientists used adult cell nuclei as opposed to the embryonic cell nuclei used in previous [sheep](#) [25] experiments. After Dolly was born, the scientists applied these techniques in genetically modified mammalian embryos. Quiescence enabled the scientists to perform genetic modifications on the [nucleus](#) [10] of the cell because growth factors were not altering the inserted DNA. In 1997, a Roslin Institute team used similar techniques to genetically modify Polly the [sheep](#) [25] to express a human protein. After the success of Dolly and Polly, some scientists worked to clone human embryos using SCNT, however there were social, ethical and legal controversies over the practice. Many disagreed with the claims that scientists could or should clone, or perhaps genetically modify, [humans](#) [30] using SCNT.

Scientists sought ways to clone human embryos without causing controversy. In 2011, Scott Noggle and his team at the New York Stem Cell Foundation in New York, New York, used SCNT to retrieve human [embryonic stem cells](#) [31]. Although, Noggle's team did not perform SCNT using the same methods that produced Dolly. In fact, Noggle and his colleagues aimed to avoid the social and ethical implications of working with human embryos. Instead of removing the [nucleus](#) [10] of the receiving [egg](#) [11] cell before transfer, the scientists kept the [egg](#) [11] [nucleus](#) [10] and inserted the donor [nucleus](#) [10] into the [egg](#) [11] cell. As a result, the embryo developed into the [blastocyst](#) [28] stage where scientists could extract [stem cells](#) [6]. The chromosome count, however, was sixty-nine as opposed to the normal forty-six, because it

contained the chromosomes from the full [nucleus](#) [10] as well as the [egg](#) [11] [nucleus](#) [10], which only contains half, or twenty-three of the chromosomes in a [zygote](#) [32]. This result meant that the [blastocyst](#) [28] could not result in a [pregnancy](#) [33] leading to birth because the cells would not progress to a further developmental state. Embryonic [stem cells](#) [6] are derived from these [blastocyst](#) [28] cells.

Scientists report that SCNT is a plausible technique for creating human [embryonic stem cells](#) [31] without extra chromosomes. In 2013, scientists in Oregon succeeded in using SCNT to reprogram somatic cells to become [embryonic stem cells](#) [31]. After examining Noggle's research, Masahito Tachibana and his team at the Oregon National Primate Research Center in Hillsboro, Oregon, used the same methods that Campbell and his team had used to clone Dolly, but they also added a few extra procedures. The key differences were that they removed the spindle apparatus, which is responsible for movement of chromosomes in cellular [mitosis](#) [34] and [meiosis](#) [35], from the donor [egg](#) [11] cell before removing the [egg](#) [11] cell [nucleus](#) [10]. They reinserted the spindle apparatus into the cell when they inserted the donor [nucleus](#) [10]. After removing the spindle apparatus, they also added caffeine, which inhibits the enzyme protein phosphatase, which activates proteins that begin cellular replication in the cytoplasm. Because the spindle apparatus was removed and the cytoplasm inactivated, the scientists could perform their procedures without risk of premature activation of the cell resulting in cellular damage and death. The results of the experiment showed that the cells altered with SCNT reached the [blastocyst](#) [28] stage and produced [viable](#) [26] embryonic stem cell lines of normal chromosome count. As of 2014, doctors use this version of SCNT for medical therapies and treatment, described as therapeutic [cloning](#) [7].

Controversies due to SCNT largely arise from the possibility of [cloning](#) [7] [humans](#) [30]. In 2003, a private company called Clonaid headquartered in Las Vegas, Nevada, claimed to have cloned the first human baby, called Eve, using SCNT. However, Clonaid did not allow scientists to perform a DNA test on Eve to confirm that she was indeed a clone, and therefore many in the scientific community doubted their claims. As of 2014, controversies arose over the possibility of human clones from SCNT. Some criticized the scientists who used SCNT to clone human [stem cells](#) [6] in Oregon. The Oregon scientists justified their research by claiming that their only goal was to produce [embryonic stem cells](#) [31] and not to produce a fully developed human being.

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In the second half of the twentieth century, scientists learned how to clone organisms in some species of mammals. Scientists have applied somatic cell nuclear transfer to clone human and mammalian embryos as a means to produce stem cells for laboratory and medical use. Somatic cell nuclear transfer (SCNT) is a technology applied in cloning, stem cell research and regenerative medicine. Somatic cells are cells that have gone through the differentiation process and are not germ cells. Somatic cells donate their nuclei, which scientists transplant into eggs after removing their nucleuses (enucleated eggs). Therefore, in SCNT, scientists replace the nucleus in an egg cell with the nucleus from a somatic cell.

Subject

Cloning ^[41] Nuclear transfer ^[42] Campbell, Keith, 1954-2012 ^[43] Wilmut, Ian ^[44] Roslin Institute ^[45] Spemann, Hans, 1869-1941 ^[46] Willadsen, S. M. (Steen M.) ^[47] Briggs, Thomas ^[48] Robert King ^[49] Genetic engineering ^[50]

Topic

Theories ^[51] Technologies ^[52] Processes ^[53]

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