Navigating Bioethical Waters: The ethical landscape behind stem cell research

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Abstract

July 5 1996 marked the emergence of limitless, scientific fantasies. Dolly the sheep was born from her surrogate mother, after being cloned by Sir Ian Wilmut and his team from a six-year-old Finn Dorset sheep [1]. Dolly was formed through genetic material being extracted from the mammary gland of the Finn Dorset sheep and placed into an enucleated egg cell, taken from a Scottish Blackface sheep [2]. An embryo was formed following a series of meiotic divisions, and 148 days (about 5 months) after being implanted into the surrogate mother's uterus, Dolly was born [3].

Dolly wasn't the first mammal to be cloned, with that title being held by two other sheep, Megan and Morag, who had been cloned a year earlier from embryonic and fetal cells [2]. However, themis didn't undermine her significance, through being the first mammal cloned from an adult cell, rather than an embryonic cell. Dolly's existence disproved past assumptions that specialized cells could only do a certain job, with Dolly being born from a specialized mammary cell which somehow held the genetic information to create an entire new sheep [4]. This sparked new potential for medicine and biology through the development and research of personalized stem cells, with researchers continuing to advance their knowledge on stem cells today.

Introduction

Human cloning can be defined as the creation of a 'genetically identical copy of a previously existing human,' or the reproduction of cloned cells / tissue from that individual [5]. Through human cloning, we can gain stem cells from the cloned blastocyst and treat these cells to differentiate into any cells we need for medical purposes. However, this understandably has ethical complications which have made it difficult for scientists to carry out lots of stem cell research.

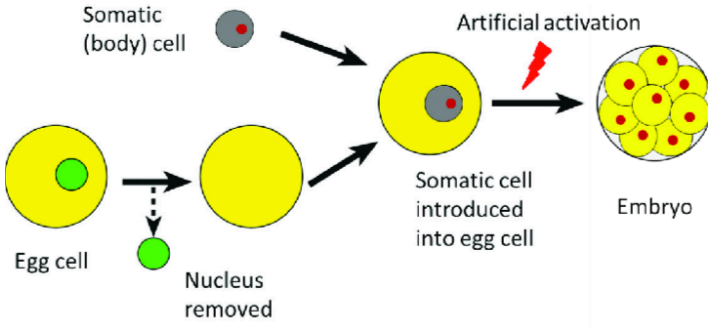
This article focuses on the more complex ethical standpoints around stem cell research through some forms of therapeutic cloning, using SCNT (Somatic cell nuclear transfer) and iPSCs (Induced pluripotent stem cells).

An insight into modern stem cell research - iPSCs and SCNT

Somatic cell nuclear transfer (SCNT) refers to the process used by both reproductive and therapeutic cloning to produce a cloned embryo. SCNT was first used by Sir Ian Wilmut and his team when cloning Dolly, the sheep:

- The nucleus which contains the organism's genetic material (DNA) of a somatic cell is removed

- The nucleus from the somatic cell is then inserted into the cytoplasm of an enucleated egg cell
- The egg which contains the nucleus stimulated with electric shocks to encourage miotic division
- After many miotic divisions, the cell forms a blastocyst, which divides further until it eventually forms an embryo [6]



(Image: Michael S. Pepper, C Gouveia) [26]

SCNT is used by scientific researchers around the world for stem cell research. They aim to obtain stem cells from the donor organism (the cloned embryo), so they can be used in regenerative medicine [6]. The in-depth process includes gaining undifferentiated stem cells from the embryo and treating them to differentiate for therapeutic purposes such as curing diseases [7].

With the use of SCNT, autologous cells can be formed, meaning the therapeutic material is cloned from the patient, allowing there to be no need for immunosuppressive treatments when differentiated cells are injected into the body [7]. With stem cell's ability to 'treat many human afflictions, including ageing, cancer, diabetes, blindness and neurodegeneration,' why is there such a lack of breakthrough research on stem cell therapy [8]?

Induced pluripotent stem cells (iPSCs) refer to cells that have been derived and reprogrammed from adult somatic cells (normally taken from a patient bone marrow) [9]. These cells have been altered through the introducing genes and other factors into the cells to make them pluripotent; this arguably makes them like embryonic stem cells, so they arguably carry the same ethical problems [9].

IPSCs are not only can be seen as unethical, but also take 3-4 weeks of careful lab work to form [10]. The process is extremely slow and inefficient and has a success rate lower than 0.1% [10]. Nonetheless, there are limitless applications for iPSCs such as regenerative medicine, disease modeling and gene therapy.

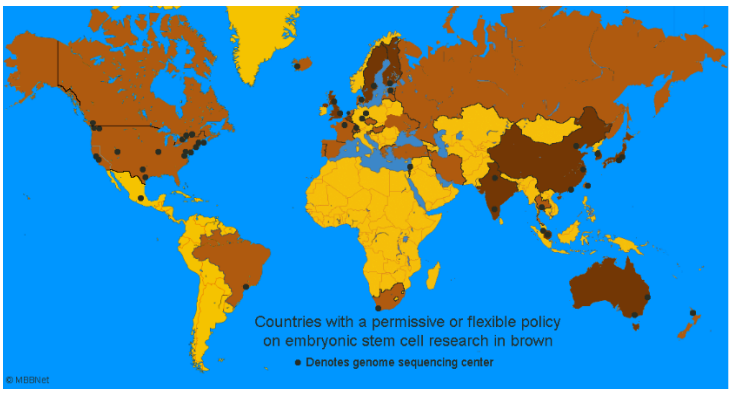
Similarly to SCNT, the main advantage of iPSCs is its ability to eliminate any possibility of immune system rejection. The iPS cells are directly generated form the somatic cell of the person's own body, so there can't be an immune response to them as the cells are genetically tailored precisely for the patient they are taken from [12]. The main problem of iPSC is the risk of mutation during the reprogramming of the somatic cells, which can lead to the formation of a tumor [11]. However, we still need to explore the ethical standpoints in the formation of pluripotent stem cells for research and regenerative science.

The ethics - SCNT

Through the process of SCNT, we can gain embryonic stem cells from a three-day old embryo. The extraction of the stem cell destroys the blastocyst; a cluster of around 180 cells growing within a petri dish [13]. The blastocyst is used as it is at such an early stage of the formation of the fetus, so the cells have not yet differentiated [13].

The ethical argument against the extraction of stem cells is the fact that the destruction of an embryo is arguably killing a fully developed human being. We can look at the position of Senator Sam Brownback, who saw 'a human embryo...as a human being just like you and me. [13]' The ethical standpoint around the destruction of embryos is so varied, with George Bush using his veto when US Congress passed a controversial bill, which permitted more funding towards research that used embryonic stem cells [14]. All these ethical considerations surrounding the formation of stem cells are difficult to forget, yet we still need to remember the immense medical and research potential they carry.

Embryonic stem cell research around the globe - SCNT



(Image: William Hoffman, MBBNet) [15]

Map Explanation [15]

- Dark Brown = 'permissive' - Allows various embryonic stem cell research techniques such as SNCT.

- Light Brown = ‘flexible’ - Lots of restrictions, with embryos only being used under extreme conditions. SCNT is completely banned with human reproductive cloning not allowed.
- Yellow = no policy or restricted policy – Outright prohibition of embryonic stem cell research
- Black Dots – Leading genome sequencing research centers in the world

The map above illustrates the flexibility around the globe when it comes to the use of embryos during stem cell research. Even in the very few countries which have leading facilities and institutions, there are massive restrictions on the usage of embryos. Even looking at Britain, who managed to vote on the easing of restrictions on the use of embryonic stem cells in 2001, we still have a measly 7 laboratories across the country [16], [17].

The various ethical considerations around the destruction of an embryo makes stem cell research difficult to legalize and even fund. However, the use of stem cells can be arguably seen as the most promising research done for regenerative medicine in the last century. Imagine the ability to cure diseases through replacing cells damaged by infection or being able to grow organs from stem cells to transplant into the thousands of patients waiting for an organ donor.

What if there was a way to form somatic stem cells without the destruction of an embryo...

The ethics - iPSCs

Pluripotent stem cells have the ability to form all three of the basic layers in our body (ectoderm/endoderm/mesoderm), which allows them to potentially produce any cell or tissue within the body [18]. There are four types of pluripotent human stem cells [19]:

- Embryonic stem cells
- Nuclear Transplant stem cells
- Parthenote stem cells
- Induced stem cells

All pluripotent human stem cells, apart from Induced stem cells, require human eggs to create. These induced pluripotent stem cells were discovered over ten years ago by Shinya Yamanaka. The Nobel Prize winner managed to revolutionize biological research by developing a technique to convert adult mature cells into stem cells using the four key genes OCT3/4, SOX2, KLF4, MYC, now known as the ‘Yamanaka factors [20].’ iPSCs as a research area has been greatly explored by thousands of researchers around the world, due to the production of the cells being non-controversial in their ability to be derived straight from adult cells rather than embryonic cells. There have been numerous applications of iPSCs in therapeutic medicine. In 2014, RIKEN (The largest scientific research institution in Japan), treated the first patient with iPSC derived retinal sheets [21]. 2 years later, Cynata Therapeutics (A biotech company), produced

iPSC derived product for the treatment of GvHD (Graft versus host disease) [21]. The unlimited medical possibilities iPSCs unlock, paired with the lack of ethical problems they face, makes IPSCs the perfect way to bring stem cell therapy to the masses.

However it is not so simple, with the main issue of iPSCs is the need for retrovirus to form these stem cells [22]. Retroviruses can insert their DNA anywhere in the human genome and trigger cancerous gene expression when transplanted into the patient [22]. Furthermore, the success rate of reprogramming somatic cells into iPSCs is around 0.1%. Not only this, but iPSCs have a strange tendency to not always differentiate, making them much less reliable and successful than embryonic stem cells [22].

Nonetheless, research into iPSCs has developed rapidly over the past few years, with scientists and researchers slowly making stem cell therapy using iPSCs available to the general public.

The pros and cons of Embryonic Stem Cells vs Induced Pluripotent Stem Cells

	Embryonic Stem Cells	Induced Pluripotent Stem Cells
Pros	• Can maintain and grow for 1 year or more in culture • Established protocols for maintenance in culture • ESCs are pluripotent cells that can generate most cell types • By studying ESCs, more can be learned about the process of development	• Abundant somatic cells of donor can be used • Issues of histocompatibility with donor/recipient transplants can be avoided • Very useful for drug development and developmental studies • Information learned from the “reprogramming” process may be transferable for in vivo therapies to reprogram damaged or diseased cells/tissues
Cons	• Process to generate ESC lines is inefficient • Unsure whether they would be rejected if used in transplants. • Therapies using ESC avenues are largely new and	• Methods for ensuring reproducibility and maintenance, as differentiated tissues are not certain. • Viruses are currently used to introduce embryonic genes and has been shown to

	much more research and testing is needed • If used directly from the ESC undifferentiated culture prep for tissue transplants, they can cause tumors (teratomas) or cancer development	cause cancers in mouse studies
Ethical Concerns	• To acquire the inner cell mass the embryo is destroyed • Risk to female donors being consented	• iPS cells have the potential to become embryos if exposed to the right conditions

(Table: University of Nebraska Medical Centre, Omaha) [25]

Stem cell therapy today

Although no one has been cured of Parkinson's disease yet, the research from institutions around the world have shown significant development in recent years with 'experimental treatment.' Earlier this year, on the 13th of February, embryonic stem cells (most likely obtained through SCNT) derived healthy, dopamine producing nerve cells, which were transplanted into a patient with Parkinson's at Skåne University Hospital, Sweden [23]. This marks an important milestone for all stem cell research, with the transplantation of the nerve cells being performed perfectly, shown by magnetic resonance imaging (MRI) [23].

The STEM – PD trial at Lund University (The first in-human trial to test the safety of stem cells for Parkinsons) is continuing to replace lost dopamine cells with healthy ones, manufactured from embryonic stem cells [23]. Their goal is to move STEM – PD from their first human trial all the way to global treatment around the world [23]. This latest success in the use of embryonic stem cells further pushes researchers around the world, with stem cells soon to unlock cures for multiple diseases, in addition to aiding with the worldwide shortage of organs.

At the start of this year, on Jan 12, University-led researchers created the first highly mature neurons from induced pluripotent stem cells (iPSCs) [24]. The usage of iPSCs made it an arduous task, with the team needing to firstly differentiate the iPSCs into motor neurons, before placing them into coatings of synthetic nanofibers containing rapidly moving dancing molecules [24]. Within the near future, researchers believe that these mature neurons can be transplanted into those suffering with spinal cord injuries as well as neurodegenerative diseases (ALS,

Parkinsons, Alzheimer's, Sclerosis) [24]. This new advancement in the usage of iPSCs allows scientists to research into ethical sound ways of using stem cells for the treatment of all diseases.

Conclusion

Stem cells use in repairing damaged cells/tissues, research into understanding diseases and testing for new drugs gives them incredible value in research and regenerative medicine. As the research for regenerate medicine improves, the success rate in the use of stem cells will gradually grow, which will hopefully loosen the tight legal grasp over the use of ESC (embryonic stem cells) and iPSCs due to their ethical problems (As seen in the table above), in either destroying and embryo or theoretically being from an embryo in iPSCs as they can be derived into an embryo.

Researcher and scientists should strive to refine existing stem cell formation techniques, and through the difficult legal ties, battle their way to the final aim of having stem cells with the ability to differentiate into any cell needed to cure any disease, form any organs to be used in transplants, and research into greater depth the difficulty in battling certain diseases.

References

[1] Weintraub, Karen. “20 Years after Dolly the Sheep Led the Way-Where Is Cloning Now?” Scientific American, July 1, 2016.

https://www.scientificamerican.com/article/20-years-after-dolly-the-sheep-led-the-way-where-is-cloning-now/.

[2] “The Life of Dolly.” Dolly the Sheep. Accessed November 26, 2023.

https://dolly.roslin.ed.ac.uk/facts/the-life-of-dolly/index.html#:~:text=Dolly%20was%20cloned%20from%20a,from%20a%20Scottish%20Blackface%20sheep

[3] “Dolly and Polly.” Encyclopedia Britannica. Accessed November 26, 2023.

https://www.britannica.com/biography/Ian-Wilmut/Dolly-and-Polly.

[4] Natural World 5 min read. “Dolly the Sheep.” National Museums Scotland. Accessed November 26, 2023.

https://www.nms.ac.uk/explore-our-collections/stories/natural-sciences/dolly-the-sheep/.

[5] “Human Cloning.” ScienceDaily. Accessed November 26, 2023.

https://www.sciencedaily.com/terms/human_cloning.htm.

[6] “Somatic Cell Nuclear Transfer.” Somatic_cell_nuclear_transfer. Accessed November 26, 2023.

https://www.bionity.com/en/encyclopedia/Somatic_cell_nuclear_transfer.html.

[7] “Therapeutic Cloning.” Therapeutic Cloning - an overview | ScienceDirect Topics. Accessed November 26, 2023.

https://www.sciencedirect.com/topics/engineering/therapeutic-cloning.

[8] Watt, Fiona M, and Ryan R Driskell. “The Therapeutic Potential of Stem Cells.” Philosophical transactions of the Royal Society of London. Series B, Biological sciences, January 12, 2010.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2842697/#:~:text=Almost%20every%20day%20there%20are,%2C%20diabetes%2C%20blindness%20and%20neurodegeneration.

[9] Ye, Lei, Cory Swingen, and Jianyi Zhang. “Induced Pluripotent Stem Cells and Their Potential for Basic and Clinical Sciences.” Current cardiology reviews, February 1, 2013.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3584308/.

[10] Ghaedi, Mahboobe, and Laura E Niklason. “Human Pluripotent Stem Cells (Ipsc) Generation, Culture, and Differentiation to Lung Progenitor Cells.” Methods in molecular biology (Clifton, N.J.), 2019.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5976544/#:~:text=To%20generate%20the%20iPSCs%2C%20each,low%20as%00.01–0.1%20%25.

[11] “Why IPSC Research Is so Important (and so Tough).” Tecan. Accessed November 27, 2023.

https://www.tecan.com/blog/why-ipsc-research-is-soimportant#:~:text=For%20example%2C%20iPSC%20are%20used,specific%20cell%20types%20and%20tissues.

[12] Lowden, Olivia. Advantages and disadvantages of induced pluripotent stem cells, November 10, 2023.

https://blog.bccresearch.com/advantages-and-disadvantages-of-induced-pluripotent-stem-cells#:~:text=iPS%20cells%20are%20generated%20from,unknown%20bodies%20and%20attacks%20them

[13] “Examining the Ethics of Embryonic Stem Cell Research.” Harvard Stem Cell Institute (HSCI). Accessed November 28, 2023.

https://hsci.harvard.edu/examining-ethics-embryonic-stem-cell-research#:~:text=Opponents%20argue%20that%20the%20research,taking%20of%20innocent%20human%20life

[14] Lenzer, Jeanne. “Bush Says He Will Veto Stem Cell Funding, despite Vote in Favour in Congress.” BMJ (Clinical research ed.), June 16, 2007.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1892464/.

[15] Stem cell policy: World stem cell map. (Image: William Hoffman, MBBNet) Accessed November 29, 2023.

https://www.mbbnet.umn.edu/scmap.html.

[16] Lachmann, P. “Stem Cell Research--Why Is It Regarded as a Threat? An Investigation of the Economic and Ethical Arguments Made against Research with Human Embryonic Stem Cells.” EMBO reports, March 2001.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1083849/.

[17] Stem cell processing, Cellular and Molecular Therapies - NHS Blood and Transplant. Accessed November 29, 2023.

https://www.nhsbt.nhs.uk/cellular-and-molecular-therapies/products-and-services/stem-cell-processing/

[18] Stem Cell Program, Pluripotent Stem Cell Research. Accessed November 29, 2023.

https://www.childrenshospital.org/research/programs/stem-cell-program-research/stem-cell-research/pluripotent-stem-cell-research#:~:text=What%20makes%20pluripotent%20stem%20cells,body%20needs%20to%20repair%20itself.

[19] Beford Research Foundation. ‘What are Induced Pluripotent Stem Cells? (iPS Cells)’ Apr 23, 2011
https://www.youtube.com/watch?v=i-QSurQWZo0

[20] Dana G. ‘Reflecting on the Discovery of the Decade: Induced Pluripotent Stem Cells.’ Accessed November 29, 2023.
https://gladstone.org/news/reflecting-discovery-decade-induced-pluripotent-stem-cells

[21] Cade Hildreth. Induced Pluripotent Stem Cell (iPS Cell) Applications in 2023. Accessed December 3, 2023.

https://bioinformant.com/ips-cell-applications/

[22] Dr. Surat, and Dr. Tomislav Mestrovic. Induced Pluripotent Stem (iPS) Cells: Discovery, Advantages and CRISPR Cas9 Gene Editing. Accessed December 3, 2023.

https://www.news-medical.net/life-sciences/Induced-Pluripotent-Stem-(iPS)-Cells-Discovery-Advantages-and-CRISPR-Cas9-Gene-Editing.aspx#:~:text=Muhammad%20Khan%20%7C%20TEDxBrentwoodCollegeSchool-,Disadvantages,trigger%20cancer-causing%20gene%20expression

[23] First patient receives milestone stem cell-based transplant for Parkinson's Disease. Feb 28, 2023
https://www.lunduniversity.lu.se/article/first-patient-receives-milestone-stem-cell-based-transplant-parkinsons-disease

[24] Amanda Morris. Mature 'lab grown' neurons hold promise for neurodegenerative disease. Jan 12, 2023

https://news.northwestern.edu/stories/2023/01/mature-lab-grown-neurons-hold-promise-for-neurodegenerative-disease/

[25] University of Nebraska Medical Center. STEM CELLS. Accessed December 5, 2023

https://www.unmc.edu/stemcells/educational-resources/prosandcons.html

[26] Michael S. Pepper, C Gouveia. Legislation governing pluripotent stem cells in South Africa. Sept 2015

https://www.researchgate.net/figure/Somatic-cell-nuclear-transfer-SCNT-SCNT-involves-the-removal-of-the-chromosomes_fig3_285619276