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**Cell transplantation therapy using pluripotent stem cells**

**Isakov N.** Pluripotent stem cells for transplantation therapy

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**Abstract**

The 2012 Nobel Prize in Physiology or Medicine was awarded jointly to Sir John B Gurdon and Shinya Yamanaka "for the discovery that mature cells can be reprogrammed to become pluripotent". Professor John Gordon who pioneered the field of somatic cell nuclear transfer was the first to show that a nucleus of a mature cell can be transplanted into an enucleated egg and give rise to a living organism. His pioneering “cloning” technique paved the way for genome reprogramming and has led to subsequent cloning of different animal species. Professor Shinya Yamanaka revolutionized the filed of stem cell production by showing that the introduction of four selected genes into cells transform them into induced pluripotent stem cells that resemble embryonic stem cells and serve as promising cells for future regenerative medicine.

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**Key words:** Stem cells; Induced pluripotent stem cells; Induced pluripotent stem cells; Somatic cell nuclear transfer; Nobel Prize

**Core tip:** The 2012 Nobel Prize in Physiology or Medicine was awarded jointly to Sir John B Gurdon and Shinya Yamanaka "for the discovery that mature cells can be reprogrammed to become pluripotent". Induced pluripotent stem (iPS) cells derived from healthy and sick patients could be a useful source for drug discovery, while healthy iPS cells could serve as a unique and highly promising source for future cell transplantation therapies and regenerative medicine.

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**COMMENTARY ON HOT TOPICS**

One of the most fascinating fields of the present biomedical research relies on the development of new technologies that enable reprograming of mature cells and induction of their de-differentiation into young or embryonic cells that can later form many different cell types. The cells formed in this process, termed induced pluripotent stem (iPS) cells, represent a promising solution for cell-based therapy and regenerative medicine.

The pioneering work of two eminent scientists in this field has recently been recognized by the Nobel committee, who decided to jointly award the 2012 Nobel Prize in Physiology or Medicine to Sir John B Gurdon and Shinya Yamanaka "for the discovery that mature cells can be reprogrammed to become pluripotent".

The two new Nobel Laureates, Professor John B Gurdon from the [Wellcome Trust](http://en.wikipedia.org/wiki/Wellcome_Trust)-[Cancer Research United](http://en.wikipedia.org/wiki/Cancer_Research_UK) Kingdom Institute for Cell Biology and Cancer (that was renamed the [Gurdon Institute](http://en.wikipedia.org/wiki/Gurdon_Institute), in his honor), at the University of Cambridge, United Kingdom, and Professor Shinya Yamanaka, from the Center for iPS Cell Research and Application at Kyoto University, Japan made groundbreaking discoveries by demonstrating that specialized somatic cells that are fully differentiated, can be reprogrammed to become pluripotent immature cells. These newly formed cells are capable of differentiating into all types of cells that generate the body’s tissues and organs. The findings of Gurdon and Yamanaka have revolutionized our understanding of how cells and organisms develop.

John Gurdon pioneered the field of somatic cell nuclear transfer. He was the first to demonstrate, in the early sixties, that cell specialization is a reversible process. In a classic experiment, Gurdon *et al*[[1](#_ENREF_1)] transplanted a nucleus from a mature Xenopus laevis intestinal cell into an enucleated Xenopus laevis egg and found that the modified egg cell developed into a normal tadpole. The phenotype of the tadpole was identical to that of the nucleus donor. Gurdon demonstrated therefore that a nucleus of a differentiated somatic cell could undergo reprogramming and acquire a state of totipotency. He further demonstrated that the adult frogs arising from the nuclei-transplanted egg were healthy and capable of reproduction[[2](#_ENREF_2),[3](#_ENREF_3)]. This experiment indicated that the DNA of the mature cell included the entire genetic information required for the development of all cells in the frog.

The discoveries by Gurdon and colleagues paved the way for additional somatic cell nuclear transfer experiments that were performed in different species, with “Dolly the sheep” being the most famous cloned animal[[4](#_ENREF_4)]. Dolly was produced by Wilmut *et al*[[4](file:///C%3A%5CDocuments%20and%20Settings%5CAdministrator%5C%E6%A1%8C%E9%9D%A2%5C2012-10-10%5C2571%5C2571-Revised%20Version%20-.docx#_ENREF_4)] who took a nucleus from an adult mammary gland cell and transferred it into an unfertilized and enucleated egg. Dolly represented a true clone since the genomic DNA of her cells, including the DNA microsatellites, were identical to that of her parent DNA, which served as the cell nucleus donor. Dolly lived a normal life and gave birth to six normal and healthy lambs. She was euthanized in 2003 because of severe arthritis and progressive lung disease. Although it was suspected that Dolly, as well as other cloned animals were destined to age prematurely, intensive health screening did not reveal abnormalities in Dolly that could result from advanced aging.

Many cell cloning attempts were performed in the past few years in a wide range of species (including mouse[[5](#_ENREF_5)], rabbit[[6](file:///C%3A%5CDocuments%20and%20Settings%5CAdministrator%5C%E6%A1%8C%E9%9D%A2%5C2012-10-10%5C2571%5C2571-Revised%20Version%20-.docx#_ENREF_5)], cat[[7](file:///C%3A%5CDocuments%20and%20Settings%5CAdministrator%5C%E6%A1%8C%E9%9D%A2%5C2012-10-10%5C2571%5C2571-Revised%20Version%20-.docx#_ENREF_5)], horse[[8](file:///C%3A%5CDocuments%20and%20Settings%5CAdministrator%5C%E6%A1%8C%E9%9D%A2%5C2012-10-10%5C2571%5C2571-Revised%20Version%20-.docx#_ENREF_5)], ferret[[9](file:///C%3A%5CDocuments%20and%20Settings%5CAdministrator%5C%E6%A1%8C%E9%9D%A2%5C2012-10-10%5C2571%5C2571-Revised%20Version%20-.docx#_ENREF_5)], and other species), using the somatic cell nuclear transfer method with variable degrees of success. These studies further substantiated Gurdon’s conclusions that the genome of adult cells contains the entire information necessary to generate living organisms.

A significant leap in the stem cell technology progress was made in 2006 by Shinya Yamanaka and colleagues who were the first to induce de-differentiation of mature cells and their conversion into immature cells that resemble embryonic stem (ES) cells. Shinya Yamanaka and his graduate student, Kazutoshi Takahashi, first compiled a large set of genes that are known to be expressed in stem cells and are suspected of accounting for the pluripotency of the human ES cells. By ectopic expression of a set of 24 individual genes in adult fibroblast, the researchers succeeded in obtaining cells that appeared to have the morphology of human ES cells. The researches than repeated the experiment multiple times, using subsets of these genes, in a search for a minimal number of genes that were sufficient for reverting the somatic cells into ES cells.

In this remarkable breakthrough study, published in 2006 by Yamanaka and Takahashi[[10](#_ENREF_10)], the researchers reported their success in converting mouse embryonic and adult fibroblasts into pluripotent stem cells by introducing a set of only four regulatory genes into the fibroblasts under ES cell culture conditions. These regulatory genes, namely octamer-binding transcription factor 3/4, sex determining region Y-box 2, v-myc myelocytomatosis viral oncogene homolog (avian), and Krüppel-like factor-4, encode transcription factors that are required and sufficient for the maintenance of the essential properties of normal ESCs. Yamanaka’s reprogrammed cells, termed ‘induced pluripotent stem cells’, exhibited the morphology and growth properties of ES cells and expressed ES cell marker genes. Upon their transplantation into nude mice, the iPS cells formed polyclonal tumors representing tissues from all three germ layers.

In a following publication by Yamanaka *et al*[[11](#_ENREF_11)], the authors demonstrated that the technology for iPS cell generation could be applied to human cells. In this study, the researchers succeeded in reprogramming adult human dermal fibroblasts to iPS cells with the same four factors they have previously used in the preparation of mouse iPS. The researchers demonstrated that the human fibroblast-derived iPS cells were similar to human ES cells in just every parameter tested, including morphology, growth behavior, surface markers, gene expression, epigenetic status of pluripotent cell-specific genes, and telomerase activity. The pluripotent human iPS cells were capable of differentiating into cell types representing all three germ layers both *in vitro* and *in vivo*. Transplantation of the iPS cells into the dorsal flank of immune compromised mice resulted in the formation of teratomas and histological examination of these tumors revealed tissues of endodermal-, mesodermal- and ectodermal- origin.

Yamanaka’s discoveries have completely changed our view of cell development, differentiation and maturation. The powerful technique he created for the reprogramming of human cells serves as a new platform for studies of fundamental questions in normal cell development. Within 6 years after its initial description, a large number of patient-specific iPS cell models were generated and characterized. Furthermore, a large number of patient-specific iPS cells prepared in the last few years from diseased human tissues generated enormous interest due to their potential use as physiological human disease models that can be studied in vitro. Studies of patient-specific iPS cells may help decipher the molecular basis of human diseases, identifying disease-related genes and proteins and determining their role in modifying cell behavior. In addition, these cells may contribute to the identification of new and novel drug targets and establish the basis for the design of new therapeutic approaches.

The pioneering work of cell reprogramming, significantly contributed to the understanding of the cellular and molecular mechanisms involved in cell reprogramming processes.. Furthermore, iPS cells derived from healthy and sick patients could be a useful source for drug discovery, while healthy iPS cells could serve as a unique and highly promising source for future cell transplantation therapies and regenerative medicine.

**REFERENCES**

1 **Gurdon JB**, Elsdale TR, Fischberg M. Sexually mature individuals of Xenopus laevis from the transplantation of single somatic nuclei. *Nature* 1958; **182**: 64-65 [PMID: 13566187]

2 **Gurdon JB**. The developmental capacity of nuclei taken from intestinal epithelium cells of feeding tadpoles. *J Embryol Exp Morphol* 1962; **10**: 622-640 [PMID: 13951335]

3 **Gurdon JB**. Adult frogs derived from the nuclei of single somatic cells. *Dev Biol* 1962; **4**: 256-273 [PMID: 13903027]

4 **Wilmut I**, Schnieke AE, McWhir J, Kind AJ, Campbell KH. Viable offspring derived from fetal and adult mammalian cells. *Nature* 1997; **385**: 810-813 [PMID: 9039911]

5 **Wakayama T**, Perry AC, Zuccotti M, Johnson KR, Yanagimachi R. Full-term development of mice from enucleated oocytes injected with cumulus cell nuclei. *Nature* 1998; **394**: 369-374 [PMID: 9690471 DOI: 10.1038/28615]

6 **Chesné P**, Adenot PG, Viglietta C, Baratte M, Boulanger L, Renard JP. Cloned rabbits produced by nuclear transfer from adult somatic cells. *Nat Biotechnol* 2002; **20**: 366-369 [PMID: 11923842 DOI: 10.1038/nbt0402-366]

7 **Shin T**, Kraemer D, Pryor J, Liu L, Rugila J, Howe L, Buck S, Murphy K, Lyons L, Westhusin M. A cat cloned by nuclear transplantation. *Nature* 2002; **415**: 859 [PMID: 11859353 DOI: 10.1038/nature723]

8 **Galli C**, Lagutina I, Crotti G, Colleoni S, Turini P, Ponderato N, Duchi R, Lazzari G. Pregnancy: a cloned horse born to its dam twin. *Nature* 2003; **424**: 635 [PMID: 12904778 DOI: 10.1038/424635a]

9 **Li Z**, Sun X, Chen J, Liu X, Wisely SM, Zhou Q, Renard JP, Leno GH, Engelhardt JF. Cloned ferrets produced by somatic cell nuclear transfer. *Dev Biol* 2006; **293**: 439-448 [PMID: 16584722]

10 **Takahashi K**, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006; **126**: 663-676 [PMID: 16904174 DOI: 10.1016/j.cell.2006.07.024]

11 **Takahashi K**, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; **131**: 861-872 [PMID: 18035408 DOI: 10.1016/j.cell.2007.11.019]

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