# The 2012 Nobel Prize in Physiology or Medicine

The 2012 Nobel Prize in physiology or medicine has been awarded to John Bertrand Gurdon and Shinya Yamanaka "for the discovery that mature cells can be reprogrammed to become pluripotent."

The 50-year-long story started in 1962 (the year Yamanaka was born), when John Gurdon used nuclear transplantation to demonstrate that frog skin and intestinal cells could spawn a new organism. In this way, fundamental evidence to the fact that the stem characteristics, lost during the development of an amphibian, can be in principle regained (Gurdon, 1962). Of course, at that time nobody discussed any therapeutic applications of the finding. More than 40 years later, an article by Shinya Yamanaka was published, in which it was demonstrated for the first time that somatic mammalian cells can also be reprogrammed to the pluripotent[1] state (Takahashi and Yamanaka, 2006). During this period of the next 40 years, a number of events that were not as sound, but still very important, occurred, which ultimately led to Yamanaka's discovery. Martin Evans pioneered the derivation of mouse embryonic stem (ES) cells in 1981 (Evans and Kaufman, 1981), which not only paved the way for the numerous studies of gene functions via gene knockout techniques (the 2007 Nobel Prize), but has also brought into light the first known type of pluripotent cells with a considerable therapeutic potential. Despite significant effort, human ES cells were obtained much later, only in 1999 (Thomson *et al.*, 1998), which allowed a number of researchers to consider the possibility of tissue replacement therapy in humans. I should also mention such a significant event as the cloning of Oct4 (Okamoto *et al.*, 1990; Scholer *et al.*, 1990), one of the central genes essential not only for the maintenance of cellular pluripotency, but also for its induction (as was subsequently demonstrated by Yamanaka).

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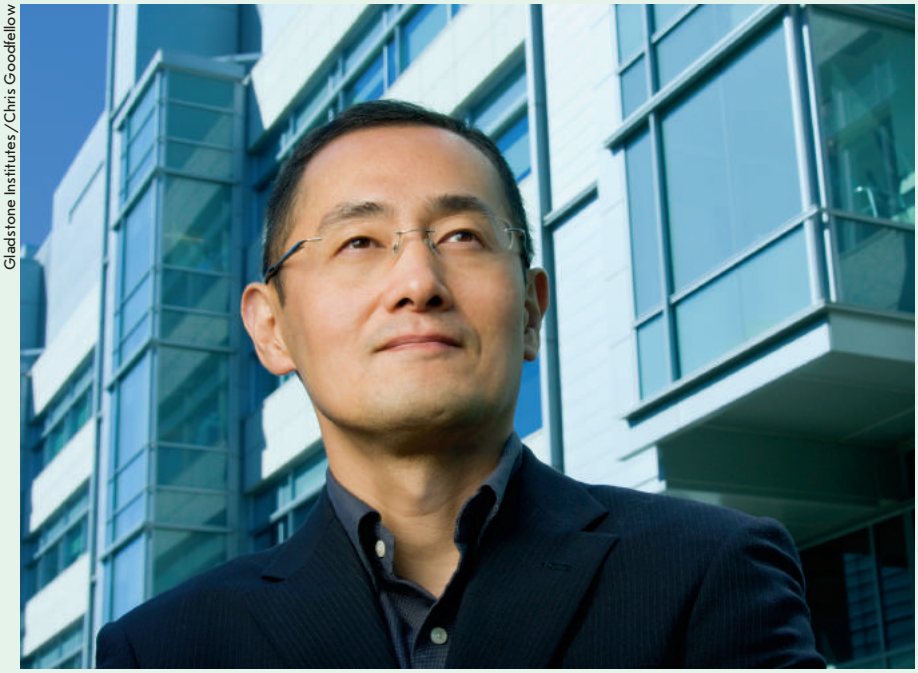
John Gurdon

Cloning of a sheep was the next milestone in cell reprogramming following Gurdon's studies; it provided the first evidence that converting mammalian somatic nuclei to the totipotent[2] state is possible.

[1] *The term "pluripotency" is used to denote the ability of cells to self-renew and differentiate to all cell types of adult mouse tissues (with the exception for two extraembryonic cell types, trophectoderm and primitive endoderm).*

[2] *In other words, the ability to give rise to all embryonic and extraembryonic cell lines; two mammalian pluripotent cell types have been known: zygote and early blastomeres.*



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Shinya Yamanaka

The reprogramming was achieved by transplanting somatic nuclei into oocyte cytoplasm (Campbell *et al.*, 1996). A series of studies showing that reprogramming can be achieved by spontaneous or induced fusion of somatic cells with ES cells is also worth mentioning (Matveeva *et al.*, 1998; Tada *et al.*, 2001; Terada *et al.*, 2002; Ying *et al.*, 2002). It became obvious that specialization of cell types during mammalian development is a reversible process.

Meanwhile, the apparent disadvantages of human ES cells came to the forefront: they were associated both with ES cell production requiring the sacrifices of human embryos and with high risks of immune rejection of differentiated derivatives of ES cells in a recipient's body.[3] Thus, the task of obtaining pluripotent stem cells from somatic cells arose in the early 2000s; this task was bound to eliminate both the ethical and practical problems associated with ES cells. Several research groups (including the one I was heading at the Max Planck Institute in Freiburg) which believed that reprogramming of somatic cells to the pluripotent state by forced gene expression was a feasible aim were doing their best, developing sophisticated approaches for the screening of reprogramming factors and selection for pluripotency. Yamanaka has drawn the final line in this pursuit. He simply picked 24 transcription factors expressed in mouse ES cells and determined the minimum combination of them sufficient for the induction pluripotency in mouse fibroblasts: Oct4, Sox2, Klf4, and cMyc (the so-called Yamanaka cocktail) (Takahashi and Yamanaka, 2006). The cells obtained in this way, named induced pluripotent stem (iPS) cells, possess characteristics that are almost identical to those of ES cells.

Six years have passed since induced pluripotency was discovered, and almost 5,000 articles have been published. These articles describe the alternative combinations of transcription factors, new methods for obtaining iPS cells in various species (including humans), propose various delivery methods (viral, plasmid, transposon, protein, RNA), use various starting somatic cell lines to obtain iPS cells, etc. A number of studies that expose the caveats of iPS cells (low generation efficiency, uncertain epigenetic status, chromosome instability, increased rate of point mutations as compared to that in ES cells, etc.) have also been published. These drawbacks postpone the introduction of iPS cells to clinics. However, it is already clear that iPS cells are indispensable both for creating *in vitro* models of a broad range of human diseases (the so-called diseases in a Petri dish) and for *in vitro* screening of drugs to treat these diseases.

Thus, the well-expected and absolutely deserved 2012 Nobel Prize has marked the start (made by Gurdon) and the finish (crossed by Yamanaka) lines in the 50-year-long marathon race in the pursuit of pluripotency. Beyond all doubts, the results of this race promise enormous benefits for mankind's health. ●

[3] *No databanks of characterized ES cells that would embrace all possible histotypes have been launched thus far.*

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Matveeva N.M., Shilov A.G., Kaftanovskaya E.M., Maximovsky

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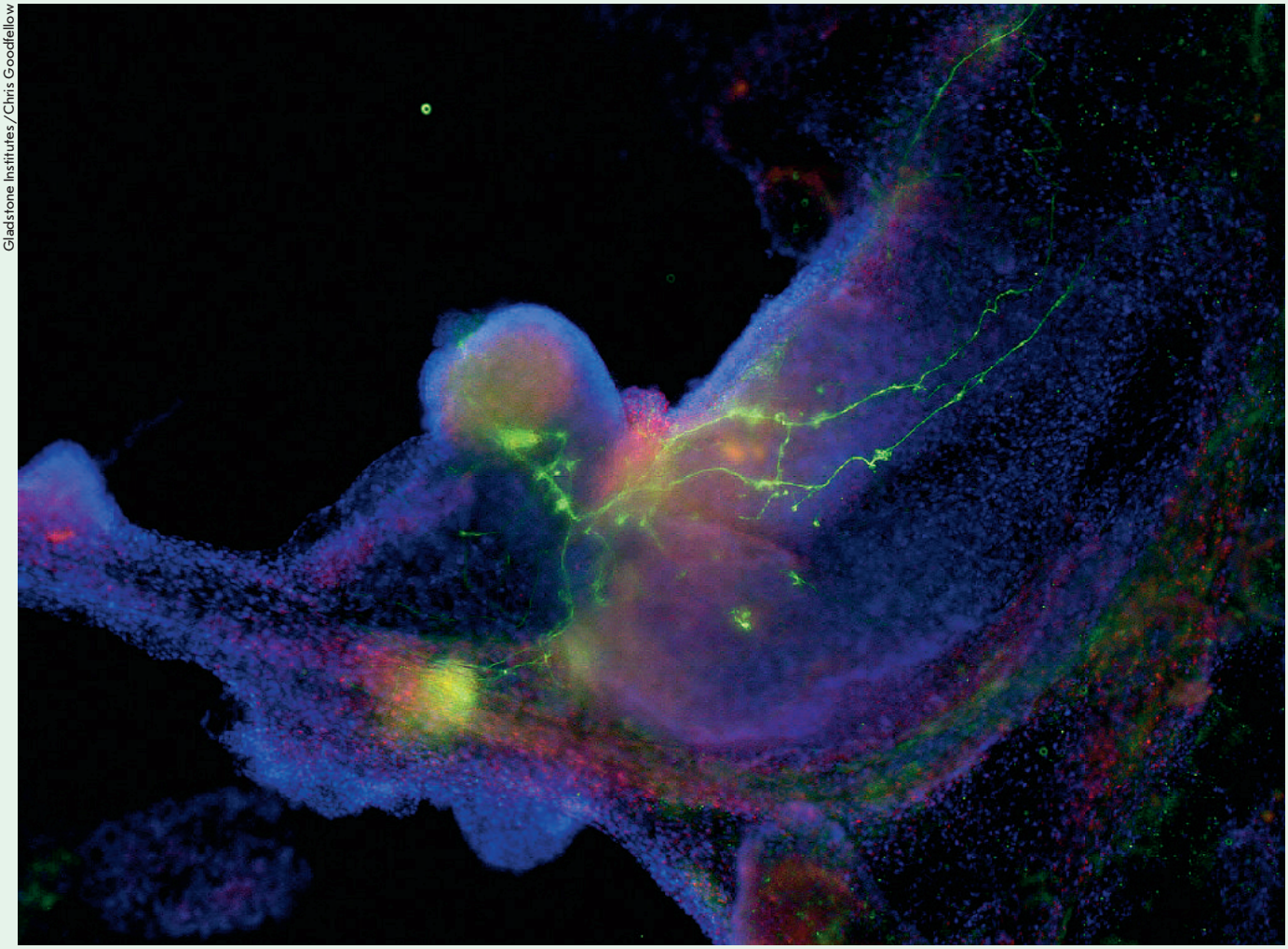

Induced pluripotent stem cells, which are known as iPS cells and act very much like embryonic stem cells, are here growing into heart cells (red) and nerve cells (green)

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