**Induced pluripotent stem cell**

From Wikipedia, the free encyclopedia

Jump to: [navigation](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#mw-navigation), [search](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#p-search)

**Induced pluripotent stem cells** (also known as **iPS** cells or **iPSCs**) are a type of [pluripotent](http://en.wikipedia.org/wiki/Pluripotent) [stem cell](http://en.wikipedia.org/wiki/Stem_cell) that can be generated directly from adult cells. The iPSC technology was pioneered by [Shinya Yamanaka](http://en.wikipedia.org/wiki/Shinya_Yamanaka)’s lab in [Kyoto](http://en.wikipedia.org/wiki/Kyoto), [Japan](http://en.wikipedia.org/wiki/Japan), who showed in 2006 that the introduction of four specific [transcription factors](http://en.wikipedia.org/wiki/Transcription_factors) could convert adult cells into pluripotent stem cells.[[1]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-ReferenceA-1) He was awarded the 2012 Nobel Prize along with Sir [John Gurdon](http://en.wikipedia.org/wiki/John_Gurdon) "for the discovery that mature cells can be reprogrammed to become pluripotent." [[2]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-2)

Pluripotent stem cells hold great promise in the field of regenerative medicine. Because they can propagate indefinitely, as well as give rise to every other cell type in the body (such as neurons, heart, pancreatic, and liver cells), they represent a single source of cells that could be used to replace those lost to damage or disease.

The most well-known type of pluripotent stem cell is the embryonic stem cell. However, since the generation of embryonic stem cells involves destruction (or at least manipulation) [[3]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-3) of the pre-implantation stage embryo, there has been much controversy surrounding their use. Further, because embryonic stem cells can only be derived from embryos, it has so far not been feasible to create patient-matched embryonic stem cell lines.

Since iPSCs can be derived directly from adult tissues, they not only bypass the need for embryos, but can be made in a patient-matched manner, which means that each individual could have their own pluripotent stem cell line. These unlimited supplies of autologous cells could be used to generate transplants without the risk of immune rejection. While the iPSC technology has not yet advanced to a stage where therapeutic transplants have been deemed safe, iPSCs are readily being used in personalized drug discovery efforts and understanding the patient-specific basis of disease.[*[citation needed](http://en.wikipedia.org/wiki/Wikipedia%3ACitation_needed%22%20%5Co%20%22Wikipedia%3ACitation%20needed)*]

Depending on the methods used, reprogramming of adult cells to obtain iPSCs may pose significant risks that could limit their use in humans. For example, if viruses are used to genomically alter the cells, the expression of cancer-causing genes "[oncogenes](http://en.wikipedia.org/wiki/Oncogenes)" may potentially be triggered. In February 2008, scientists announced the discovery of a technique that could remove oncogenes after the induction of pluripotency, thereby increasing the potential use of iPS cells in human diseases.[[4]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-urlCancer_threat_removed_from_stem_cells.2C_scientists_say_-_Los_Angeles_Times-4) In April 2009, it was demonstrated that generation of iPS cells is possible without any genetic alteration of the adult cell: a repeated treatment of the cells with certain proteins channeled into the cells via [poly-arginine anchors](http://en.wikipedia.org/wiki/Cell_penetrating_peptide) was sufficient to induce pluripotency.[[5]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-urlGeneration_of_Induced_Pluripotent_Stem_Cells_Using_Recombinant_Proteins-5) The acronym given for those iPSCs is **piPSCs** (protein-induced pluripotent stem cells).

**Contents**

* [1 Production of iPSCs](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Production_of_iPSCs)
	+ [1.1 First generation](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#First_generation)
	+ [1.2 Second generation in mice](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Second_generation_in_mice)
		- [1.2.1 Two-fathered mice](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Two-fathered_mice)
	+ [1.3 Human induced pluripotent stem cells](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Human_induced_pluripotent_stem_cells)
		- [1.3.1 Generation from human fibroblasts](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Generation_from_human_fibroblasts)
		- [1.3.2 Generation from human renal epithelial cells in urine](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Generation_from_human_renal_epithelial_cells_in_urine)
	+ [1.4 Limitations of the transcription factor approach](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Limitations_of_the_transcription_factor_approach)
	+ [1.5 Alternative approaches](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Alternative_approaches)
		- [1.5.1 Mimicking transcription factors with chemicals](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Mimicking_transcription_factors_with_chemicals)
		- [1.5.2 Alternate vectors](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Alternate_vectors)
		- [1.5.3 Stimulus-Triggered Acquisition of Pluripotency Cell](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Stimulus-Triggered_Acquisition_of_Pluripotency_Cell)
		- [1.5.4 RNA molecules](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#RNA_molecules)
	+ [1.6 Genes of induction](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Genes_of_induction)
* [2 Identity](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Identity)
* [3 Safety for regenerative medicine](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Safety_for_regenerative_medicine)
* [4 An open future](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#An_open_future)
* [5 Medical research](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Medical_research)
	+ [5.1 Disease modeling and drug development](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Disease_modeling_and_drug_development)
	+ [5.2 Organ synthesis](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Organ_synthesis)
	+ [5.3 Tissue repair](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Tissue_repair)
	+ [5.4 Red blood cells](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Red_blood_cells)
* [6 Clinical trial](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#Clinical_trial)
* [7 See also](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#See_also)
* [8 References](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#References)
* [9 External links](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#External_links)

**Production of iPSCs[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=1" \o "Edit section: Production of iPSCs)]**

*See also:* [*Reprogramming*](http://en.wikipedia.org/wiki/Reprogramming)



**A scheme of the generation of induced pluripotent stem (IPS) cells.** (1)Isolate and culture donor cells. (2)Transfect stem cell-associated genes into the cells by viral vectors. Red cells indicate the cells expressing the exogenous genes. (3)Harvest and culture the cells according to ES cell culture, using mitotically inactivated [feeder cells](http://en.wikipedia.org/wiki/Feeder_cell) (lightgray). (4)A small subset of the transfected cells become iPS cells and generate ES-like colonies.

iPSCs are typically derived by introducing a specific set of pluripotency-associated genes, or “reprogramming factors”, into a given cell type. The original set of reprogramming factors (also dubbed Yamanaka factors) are the genes Oct4 (Pou5f1), Sox2, cMyc, and Klf4. While this combination is most conventional in producing iPSCs, each of the factors can be functionally replaced by related transcription factors, miRNAs, small molecules, or even non-related genes such as lineage specifiers.

iPSC derivation is typically a slow and inefficient process, taking 1–2 weeks for mouse cells and 3–4 weeks for human cells, with efficiencies around 0.01%–0.1%. However, considerable advances have been made in improving the efficiency and the time it takes to obtain iPSCs. Upon introduction of reprogramming factors, cells begin to form colonies that resemble pluripotent stem cells, which can be isolated based on their morphology, conditions that select for their growth, or through expression of surface markers or [reporter genes](http://en.wikipedia.org/wiki/Reporter_gene).

**First generation[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=2" \o "Edit section: First generation)]**

Induced pluripotent stem cells were first generated by [Shinya Yamanaka](http://en.wikipedia.org/wiki/Shinya_Yamanaka)'s team at [Kyoto University](http://en.wikipedia.org/wiki/Kyoto_University), Japan, in 2006.[[1]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-ReferenceA-1) Their hypothesis was that genes important to embryonic stem cell function might be able to induce an embryonic state in adult cells. They began by choosing twenty-four genes that were previously identified as important in embryonic stem cells, and used retroviruses to deliver these genes to fibroblasts from mice. The mouse fibroblasts were engineered so that any cells that reactivated the ESC-specific gene, Fbx15, could be isolated using antibiotic selection.

Upon delivery of all twenty-four factors, colonies emerged that had reactivated the Fbx15 reporter, resembled ESCs, and could propagate indefinitely. They then narrowed their candidates by removing one factor at a time from the pool of twenty-four. By this process, they identified four factors, Oct4, Sox2, cMyc, and Klf4, which as a group were both necessary and sufficient to obtain ESC-like colonies under selection for reactivation of Fbx15.

Similar to ESCs, these first-generation iPSCs showed unlimited self-renewal and demonstrated pluripotency by contributing to lineages from all three germ layers in the context of embryoid bodies, teratomas, fetal chimeras. However, the molecular makeup of these cells, including gene expression and epigenetic marks, was somewhere between that of a fibroblast and an ESC, and the cells also failed to produce viable [chimeras](http://en.wikipedia.org/wiki/Chimera_%28genetics%29) when injected into developing embryos.

**Second generation in mice[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=3" \o "Edit section: Second generation in mice)]**

In June 2007, the same group published a breakthrough study along with two other independent research groups from [Harvard](http://en.wikipedia.org/wiki/Harvard), [MIT](http://en.wikipedia.org/wiki/MIT), and the [University of California, Los Angeles](http://en.wikipedia.org/wiki/University_of_California%2C_Los_Angeles), showing successful reprogramming of mouse fibroblasts into iPS cells and even producing viable chimera. These cell lines were also derived from mouse fibroblasts by retroviral mediated reactivation of the same four endogenous pluripotent factors, but the researchers now selected a different marker for detection. Instead of Fbx15, they used [Nanog](http://en.wikipedia.org/wiki/Nanog) which is an important gene in ESCs. DNA methylation patterns and production of viable chimeras (and thereby contributing to subsequent germ-line production) indicated that Nanog is a major determinant of cellular pluripotency.[[1]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-ReferenceA-1)[[6]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-6)[[7]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-7)[[8]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-8)[[9]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-9)

Unfortunately, two of the four genes used (namely, c-Myc and KLF4) are [oncogenic](http://en.wikipedia.org/wiki/Oncogenic), and 20% of the chimeric mice developed cancer. In a later study, Yamanaka reported that one can create iPSCs even without c-Myc. The process takes longer and is not as efficient, but the resulting chimeras didn't develop cancer.[[10]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-swaminathan-10)

Induced pluripotent cells have been made from adult stomach, liver, skin cells, blood cells, prostate cells and urinary tract cells.[[11]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-11)

**Two-fathered mice[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=4" \o "Edit section: Two-fathered mice)]**

Reproductive scientists in [University of Texas MD Anderson Cancer Center](http://en.wikipedia.org/wiki/University_of_Texas_MD_Anderson_Cancer_Center) have created mice with [nuclear DNA](http://en.wikipedia.org/wiki/Nuclear_DNA) (nDNA) solely from two fathers, using iPS technology.[[12]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-slasdot-12)[[13]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-bioreprod-13) Foetal [fibroblasts](http://en.wikipedia.org/wiki/Fibroblast) from one father (XY) were cultivated and one percent of the resultant cells had spontaneously lost a [Y-chromosome](http://en.wikipedia.org/wiki/Y-chromosome); like an individual with [Turner Syndrome](http://en.wikipedia.org/wiki/Turner_Syndrome) (X0).[[14]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-mdaily-14) These cells were injected in female [blastocysts](http://en.wikipedia.org/wiki/Blastocyst) (XX), which gestated in surrogate mothers to form female [chimeras](http://en.wikipedia.org/wiki/Chimera_%28genetics%29) (X0/XX). When these mated with male mice (XY), some of the offspring had nDNA from the original father and also from the mated male but not from the female blastocysts or the surrogate mother. Both male and female two-fathered mice were viable.

**Human induced pluripotent stem cells[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=5" \o "Edit section: Human induced pluripotent stem cells)]**

**Generation from human fibroblasts[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=6" \o "Edit section: Generation from human fibroblasts)]**

In November 2007, a milestone was achieved[[15]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-nature-15)[[16]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-16) by creating iPSCs from adult human cells; two independent research teams' studies were released – one in [*Science*](http://en.wikipedia.org/wiki/Science_%28journal%29) by [James Thomson](http://en.wikipedia.org/wiki/James_Thomson_%28cell_biologist%29) at [University of Wisconsin–Madison](http://en.wikipedia.org/wiki/University_of_Wisconsin%E2%80%93Madison)[[17]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-17) and another in [*Cell*](http://en.wikipedia.org/wiki/Cell_%28journal%29) by Shinya Yamanaka and colleagues at Kyoto University, Japan.[[18]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-18) With the same principle used earlier in mouse models, Yamanaka had successfully transformed human fibroblasts into pluripotent stem cells using the same four pivotal genes: Oct3/4, Sox2, Klf4, and c-Myc with a [retroviral](http://en.wikipedia.org/wiki/Retrovirus) system. Thomson and colleagues used OCT4, SOX2, NANOG, and a different gene LIN28 using a [lentiviral](http://en.wikipedia.org/wiki/Lentivirus) system.

**Generation from human renal epithelial cells in urine[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=7" \o "Edit section: Generation from human renal epithelial cells in urine)]**

On 8 November 2012, researchers from Austria, Hong Kong and China presented a protocol for generating human iPSCs from exfoliated renal epithelial cells present in urine on [Nature Protocols](http://en.wikipedia.org/wiki/Nature_Protocols).[[19]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-urinecell-19) This method of acquiring donor cells is comparatively less invasive and simple. The team reported the induction procedure to take less time, around 2 weeks for the urinary cell culture and 3 to 4 weeks for the reprogramming; and higher yield, up to 4% using retroviral delivery of exogenous factors. Urinary iPSCs (UiPSCs) were found to show good differentiation potential, and thus represent an alternative choice for producing pluripotent cells from normal individuals or patients with genetic diseases, including those affecting the kidney.[[19]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-urinecell-19)

**Limitations of the transcription factor approach[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=8" \o "Edit section: Limitations of the transcription factor approach)]**

Although the traditional method using [transcription factors](http://en.wikipedia.org/wiki/Transcription_factors) such as [Oct3/4](http://en.wikipedia.org/wiki/Oct3/4), [Sox2](http://en.wikipedia.org/wiki/Sox2), [c-Myc](http://en.wikipedia.org/wiki/C-Myc), etc. pioneered by Yamanaka and Thomson was good proof of concept that [somatic](http://en.wikipedia.org/wiki/Somatic) cells can be reprogrammed to iPS cells, there are still many key challenges for this method to overcome:

1. Throughput: the throughput of successfully reprogrammed cells has been incredibly low. For example, the rate at which [somatic](http://en.wikipedia.org/wiki/Somatic) cells were reprogrammed into iPS cells in the Yamanaka mouse study was 0.01–0.1%.[[1]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-ReferenceA-1) The low efficiency rate may reflect the need for precise timing, balance, and absolute levels of expression of the reprogramming genes. It may also suggest a need for rare genetic and/or epigenetic changes in the original [somatic](http://en.wikipedia.org/wiki/Somatic) cell population or in the prolonged culture. However, recently a path was found for efficient reprogramming which required downregulation of the [nucleosome](http://en.wikipedia.org/wiki/Nucleosome) remodeling and deacetylation ([NuRD](http://en.wikipedia.org/wiki/NuRD)) complex. Overexpression of Mbd3, a subunit of NuRD, inhibits induction of iPSCs. Depletion of Mbd3, on the other hand, improves reprogramming efficiency,[[20]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell%22%20%5Cl%20%22cite_note-20) that results in deterministic and synchronized iPS cell reprogramming (near 100% efficiency within seven days from mouse and human cells).[[21]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-21)
2. Genomic Insertion: genomic integration of the [transcription factors](http://en.wikipedia.org/wiki/Transcription_factors) limits the utility of the [transcription factor](http://en.wikipedia.org/wiki/Transcription_factor) approach because of the risk of mutations being inserted into the target cell’s genome.[[22]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-Switching_cell_fate-22) A common strategy for avoiding genomic insertion has been to use a different vector for input. [Plasmids](http://en.wikipedia.org/wiki/Plasmid), [adenoviruses](http://en.wikipedia.org/wiki/Adenovirus), and [transposon](http://en.wikipedia.org/wiki/Transposon) vectors have all been explored, but these often come with the tradeoff of lower throughput.[[23]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-23)[[24]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-24)[[25]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-25)
3. Tumors: another main challenge was mentioned above – some of the reprogramming factors are [oncogenes](http://en.wikipedia.org/wiki/Oncogenes) that bring on a potential tumor risk. Inactivation or deletion of the tumor suppressor p53, which is the master regulator of cancer, significantly increases reprogramming efficiency.[[26]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-26) Thus there seems to be a tradeoff between reprogramming efficiency and tumor generation.
4. Incomplete reprogramming: reprogramming also faces the challenge of completeness. This is particularly challenging because the genome-wide epigenetic code must be reformatted to that of the target cell type in order to fully reprogram a cell. However, three separate groups were able to find mouse embryonic [fibroblast](http://en.wikipedia.org/wiki/Fibroblast) (MEF)-derived iPS cells that could be injected into [tetraploid](http://en.wikipedia.org/wiki/Tetraploid) [blastocysts](http://en.wikipedia.org/wiki/Blastocysts) and resulted in the live birth of mice derived entirely from iPS cells, thus ending the debate over the equivalence of embryonic stem cells (ESCs) and iPS with regard to pluripotency.[[27]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-27)

The table at right summarizes the key strategies and techniques used to develop iPS cells over the past half-decade. Rows of similar colors represents studies that used similar strategies for reprogramming.



This timeline summarizes the key strategies and techniques used to develop iPS cells over the past half-decade. Rows of similar colors represents studies that used similar strategies for reprogramming.

**Alternative approaches[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=9" \o "Edit section: Alternative approaches)]**

**Mimicking transcription factors with chemicals[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=10" \o "Edit section: Mimicking transcription factors with chemicals)]**

One of the main strategies for avoiding problems (1) and (2) has been to use small compounds that can mimic the effects of transcription factors. These molecule compounds can compensate for a reprogramming factor that does not effectively target the genome or fails at reprogramming for another reason; thus they raise reprogramming efficiency. They also avoid the problem of genomic integration, which in some cases contributes to tumor genesis. Key studies using such strategy were conducted in 2008. Melton et al. studied the effects of histone deacetylase (HDAC) inhibitor valproic acid. They found that it increased reprogramming efficiency 100-fold (compared to Yamanaka’s traditional [transcription factor](http://en.wikipedia.org/wiki/Transcription_factor) method).[[28]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-28) The researchers proposed that this compound was mimicking the signaling that is usually caused by the [transcription factor](http://en.wikipedia.org/wiki/Transcription_factor) c-Myc. A similar type of compensation mechanism was proposed to mimic the effects of [Sox2](http://en.wikipedia.org/wiki/Sox2). In 2008, Ding et al. used the inhibition of histone methyl transferase (HMT) with BIX-01294 in combination with the activation of [calcium channels](http://en.wikipedia.org/wiki/Calcium_channels) in the plasma membrane in order to increase reprogramming efficiency.[[29]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-29) Deng et al. of Beijing University reported on July 2013 that induced pluripotent stem cells can be created without any genetic modification. They used a cocktail of seven small-molecule compounds including DZNep to induce the mouse somatic cells into stem cells which they called CiPS cells with the efficiency – at 0.2% – comparable to those using standard iPSC production techniques. The CiPS cells were introduced into developing mouse embryos and were found to contribute to all major cells types, proving its pluripotency.[[30]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-30)[[31]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-31)

Ding et al. demonstrated an alternative to [transcription factor](http://en.wikipedia.org/wiki/Transcription_factor) reprogramming through the use of drug-like chemicals. By studying the MET ([mesenchymal-epithelial transition](http://en.wikipedia.org/wiki/Mesenchymal-epithelial_transition)) process in which fibroblasts are pushed to a stem-cell like state, Ding’s group identified two chemicals – ALK5 inhibitor SB431412 and MEK (mitogen-activated protein kinase) inhibitor PD0325901 – which was found to increase the efficiency of the classical genetic method by 100 fold. Adding a third compound known to be involved in the cell survival pathway, Thiazovivin further increases the efficiency by 200 fold. Using the combination of these three compounds also decrease the reprogramming process of the human fibroblasts from four weeks to two weeks. [[32]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-name-32)[[33]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-33)

**Alternate vectors[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=11" \o "Edit section: Alternate vectors)]**

Another key strategy for avoiding problems such as tumor genesis and low throughput has been to use alternate forms of vectors: [adenovirus](http://en.wikipedia.org/wiki/Adenovirus), [plasmids](http://en.wikipedia.org/wiki/Plasmids), and naked DNA and/or protein compounds.

In 2008, Hochedlinger et al. used an [adenovirus](http://en.wikipedia.org/wiki/Adenovirus) to transport the requisite four [transcription factors](http://en.wikipedia.org/wiki/Transcription_factors) into the DNA of skin and liver cells of mice, resulting in cells identical to ESCs. The [adenovirus](http://en.wikipedia.org/wiki/Adenovirus) is unique from other vectors like viruses and retroviruses because it does not incorporate any of its own genes into the targeted host and avoids the potential for insertional mutagenesis.[[34]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-34) In 2009, Freed et al. demonstrated successful reprogramming of human fibroblasts to iPS cells.[[35]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-35) Another advantage of using [adenoviruses](http://en.wikipedia.org/wiki/Adenoviruses) is that they only need to present for a brief amount of time in order for effective reprogramming to take place.

Also in 2008, Yamanaka et al. found that they could transfer the four necessary genes with a plasmid.[[36]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-36) The Yamanaka group successfully reprogrammed mouse cells by transfection with two plasmid constructs carrying the reprogramming factors; the first plasmid expressed c-Myc, while the second expressed the other three factors ([Oct4](http://en.wikipedia.org/wiki/Oct4), Klf4, and [Sox2](http://en.wikipedia.org/wiki/Sox2)). Although the plasmid methods avoid viruses, they still require cancer-promoting genes to accomplish reprogramming. The other main issue with these methods is that they tend to be much less efficient compared to retroviral methods. Furthermore, transfected [plasmids](http://en.wikipedia.org/wiki/Plasmids) have been shown to integrate into the host genome and therefore they still pose the risk of insertional mutagenesis. Because non-retroviral approaches have demonstrated such low efficiency levels, researchers have attempted to effectively rescue the technique with what is known as the piggyBac [transposon](http://en.wikipedia.org/wiki/Transposon) system. The lifecycle of this system is shown below. Several studies have demonstrated that this system can effectively deliver the key reprogramming factors without leaving any footprint mutations in the host cell genome. As demonstrated in the figure, the piggyBac [transposon](http://en.wikipedia.org/wiki/Transposon) system involves the re-excision of exogenous genes, which eliminates issues like insertional mutagenesis



Lifecycle of the Piggybac Transposon System

**Stimulus-Triggered Acquisition of Pluripotency Cell[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=12" \o "Edit section: Stimulus-Triggered Acquisition of Pluripotency Cell)]**

*Main article:* [*Stimulus-triggered acquisition of pluripotency*](http://en.wikipedia.org/wiki/Stimulus-triggered_acquisition_of_pluripotency)

In January 2014 two article were published claiming that a type of pluripotent stem cell can be generated by subjecting the cells to certain types of stress (bacterial toxin, a low pH of 5.7, or physical squeezing); the resulting cells were called [Stimulus-triggered acquisition of pluripotency](http://en.wikipedia.org/wiki/Stimulus-triggered_acquisition_of_pluripotency) cells.[[37]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-37)

In light of difficulties that other labs had replicating the results of the surprising study, in March 2014, one of the co-authors has called for the articles to be retracted.[[38]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-38) On 4 June 2014, the lead author, [Obokata](http://en.wikipedia.org/wiki/Obokata) agreed to retract both the papers [[39]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-retract-39) after she was found to have committed ‘research misconduct’ as concluded in an investigation by [RIKEN](http://en.wikipedia.org/wiki/RIKEN) on 1 April 2014.[[40]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-40)

**RNA molecules[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=13" \o "Edit section: RNA molecules)]**

Studies by Blelloch et al. in 2009 demonstrated that expression of ES cell-specific [microRNA](http://en.wikipedia.org/wiki/MicroRNA) molecules (such as miR-291, miR-294 and miR-295) enhances the efficiency of induced pluripotency by acting downstream of c-Myc .[[41]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell%22%20%5Cl%20%22cite_note-41) More recently (in April 2011), Morrisey et al. demonstrated another method using [microRNA](http://en.wikipedia.org/wiki/MicroRNA) that improved the efficiency of reprogramming to a rate similar to that demonstrated by Ding. [MicroRNAs](http://en.wikipedia.org/wiki/MicroRNA) are short RNA molecules that bind to complementary sequences on messenger RNA and block expression of a gene. Morrisey’s team worked on microRNAs in lung development, and hypothesized that their [microRNAs](http://en.wikipedia.org/wiki/MicroRNA) perhaps blocked expression of repressors of Yamanaka’s four transcription factors. Possible mechanisms by which microRNAs can induce reprogramming even in the absence of added exogenous transcription factors, and how variations in microRNA expression of iPS cells can predict their differentiation potential discussed by Xichen Bao et al.[[42]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell%22%20%5Cl%20%22cite_note-42)

**Genes of induction[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=14" \o "Edit section: Genes of induction)]**

[[*citation needed*](http://en.wikipedia.org/wiki/Wikipedia%3ACitation_needed)]

The generation of iPS cells is crucially dependent on the genes used for the induction.

[Oct-3/4](http://en.wikipedia.org/wiki/Oct-3/4) and certain members of the [Sox gene family](http://en.wikipedia.org/wiki/SOX_genes) (Sox1, Sox2, Sox3, and Sox15) have been identified as crucial transcriptional regulators involved in the induction process whose absence makes induction impossible. Additional genes, however, including certain members of the [Klf family](http://en.wikipedia.org/wiki/Kruppel-like_factors) (Klf1, Klf2, Klf4, and Klf5), the [Myc family](http://en.wikipedia.org/wiki/Myc) (c-myc, L-myc, and N-myc), [Nanog](http://en.wikipedia.org/wiki/Nanog), and [LIN28](http://en.wikipedia.org/wiki/LIN28), have been identified to increase the induction efficiency.

* [**Oct-3/4**](http://en.wikipedia.org/wiki/Oct-3/4) (Pou5f1) Oct-3/4 is one of the family of [octamer ("Oct") transcription factors](http://en.wikipedia.org/wiki/Octamer_transcription_factor), and plays a crucial role in maintaining pluripotency. The absence of Oct-3/4 in Oct-3/4+ cells, such as [blastomeres](http://en.wikipedia.org/wiki/Blastomere) and [embryonic stem cells](http://en.wikipedia.org/wiki/Embryonic_stem_cell), leads to spontaneous [trophoblast](http://en.wikipedia.org/wiki/Trophoblast) differentiation, and presence of Oct-3/4 thus gives rise to the pluripotency and differentiation potential of embryonic stem cells. Various other genes in the "Oct" family, including Oct-3/4's close relatives, [Oct1](http://en.wikipedia.org/wiki/Oct1) and [Oct6](http://en.wikipedia.org/wiki/Oct6), fail to elicit induction, thus demonstrating the exclusiveness of Oct-3/4 to the induction process.
* [**Sox family**](http://en.wikipedia.org/wiki/SOX_genes): The Sox family of genes is associated with maintaining pluripotency similar to Oct-3/4, although it is associated with multipotent and unipotent stem cells in contrast with Oct-3/4, which is exclusively expressed in pluripotent stem cells. While [Sox2](http://en.wikipedia.org/wiki/Sox2) was the initial gene used for induction by Yamanaka et al., Jaenisch et al., and Thomson et al., other genes in the Sox family have been found to work as well in the induction process. [Sox1](http://en.wikipedia.org/wiki/Sox1) yields iPS cells with a similar efficiency as Sox2, and genes [Sox3](http://en.wikipedia.org/wiki/Sox3), [Sox15](http://en.wikipedia.org/wiki/Sox15), and [Sox18](http://en.wikipedia.org/wiki/Sox18) also generate iPS cells, although with decreased efficiency.
* [**Klf family**](http://en.wikipedia.org/wiki/Kruppel-like_factors): [Klf4](http://en.wikipedia.org/wiki/Klf4) of the Klf family of genes was initially identified by Yamanaka et al. and confirmed by Jaenisch et al. as a factor for the generation of mouse iPS cells and was demonstrated by Yamanaka et al. as a factor for generation of human iPS cells. However, Thomson et al. reported that Klf4 was unnecessary for generation of human iPS cells and in fact failed to generate human iPS cells. [Klf2](http://en.wikipedia.org/wiki/Klf2) and Klf4 were found to be factors capable of generating iPS cells, and related genes [Klf1](http://en.wikipedia.org/wiki/Klf1) and [Klf5](http://en.wikipedia.org/wiki/Klf5) did as well, although with reduced efficiency.
* [**Myc family**](http://en.wikipedia.org/wiki/Myc): The Myc family of genes are [proto-oncogenes](http://en.wikipedia.org/wiki/Protooncogene) implicated in cancer. Yamanaka et al. and Jaenisch et al. demonstrated that c-myc is a factor implicated in the generation of mouse iPS cells and Yamanaka et al. demonstrated it was a factor implicated in the generation of human iPS cells. However, Thomson et al., Yamanaka et al. Usage of the "myc" family of genes in induction of iPS cells is troubling for the eventuality of iPS cells as clinical therapies, as 25% of mice transplanted with c-myc-induced iPS cells developed lethal [teratomas](http://en.wikipedia.org/wiki/Teratoma). [N-myc](http://en.wikipedia.org/wiki/N-myc) and [L-myc](http://en.wikipedia.org/wiki/L-myc) have been identified to induce instead of c-myc with similar efficiency.
* [**Nanog**](http://en.wikipedia.org/wiki/Nanog): In embryonic stem cells, Nanog, along with Oct-3/4 and Sox2, is necessary in promoting pluripotency. Therefore, it was surprising when Yamanaka et al. reported that Nanog was unnecessary for induction although Thomson et al. has reported it is possible to generate iPS cells with Nanog as one of the factors.
* [**LIN28**](http://en.wikipedia.org/wiki/LIN28): LIN28 is an [mRNA binding protein](http://en.wikipedia.org/wiki/RNA-binding_protein) expressed in [embryonic stem cells](http://en.wikipedia.org/wiki/Embryonic_stem_cell) and embryonic carcinoma cells associated with differentiation and proliferation. Thomson et al. demonstrated it is a factor in iPSC generation, although it is unnecessary.
* [**Glis1**](http://en.wikipedia.org/wiki/Glis1): Glis1 is transcription factor that can be used with Oct-3/4, Sox2 and Klf4 to induce pluripotency. It poses numerous advantages when used instead of C-myc.[[43]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-Maekawa_M_et_al-43)

**Identity[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=15" \o "Edit section: Identity)]**

Induced pluripotent stem cells are similar to natural pluripotent stem cells, such as [embryonic stem (ES) cells](http://en.wikipedia.org/wiki/Embryonic_stem_cell), in many aspects, such as the expression of certain stem cell genes and proteins, [chromatin methylation](http://en.wikipedia.org/wiki/DNA_methylation) patterns, doubling time, [embryoid body](http://en.wikipedia.org/wiki/Embryoid_body) formation, [teratoma](http://en.wikipedia.org/wiki/Teratoma) formation, viable [chimera](http://en.wikipedia.org/wiki/Chimera_%28genetics%29) formation, and potency and differentiability, but the full extent of their relation to natural pluripotent stem cells is still being assessed.[[44]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-cell.com-44)

Gene expression and genome-wide H3K4me3 and H3K27me3 were found to be extremely similar between ES and iPS cells.[[45]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-45)[[*citation needed*](http://en.wikipedia.org/wiki/Wikipedia%3ACitation_needed)] The generated iPSCs were remarkably similar to naturally isolated pluripotent stem cells (such as mouse and human [embryonic stem cells](http://en.wikipedia.org/wiki/Embryonic_stem_cell), mESCs and hESCs, respectively) in the following respects, thus confirming the identity, authenticity, and pluripotency of iPSCs to naturally isolated pluripotent stem cells:

* Cellular biological properties
	+ Morphology: iPSCs were morphologically similar to ESCs. Each cell had round shape, large [nucleolus](http://en.wikipedia.org/wiki/Nucleolus) and scant [cytoplasm](http://en.wikipedia.org/wiki/Cytoplasm). Colonies of iPSCs were also similar to that of ESCs. Human iPSCs formed sharp-edged, flat, tightly packed colonies similar to hESCs and mouse iPSCs formed the colonies similar to mESCs, less flat and more aggregated colonies than that of hESCs.
	+ Growth properties: Doubling time and [mitotic](http://en.wikipedia.org/wiki/Mitosis) activity are cornerstones of ESCs, as stem cells must self-renew as part of their definition. iPSCs were mitotically active, actively self-renewing, proliferating, and dividing at a rate equal to ESCs.
	+ Stem cell markers: iPSCs expressed cell surface antigenic markers expressed on ESCs. Human iPSCs expressed the markers specific to hESC, including SSEA-3, SSEA-4, TRA-1-60, TRA-1-81, TRA-2-49/6E, and Nanog. Mouse iPSCs expressed SSEA-1 but not SSEA-3 nor SSEA-4, similarly to mESCs.
	+ Stem Cell Genes: iPSCs expressed genes expressed in undifferentiated ESCs, including Oct-3/4, Sox2, Nanog, GDF3, REX1, FGF4, ESG1, DPPA2, DPPA4, and hTERT.
	+ Telomerase activity: [Telomerases](http://en.wikipedia.org/wiki/Telomerase) are necessary to sustain cell division unrestricted by the [Hayflick limit](http://en.wikipedia.org/wiki/Hayflick_limit) of ~50 cell divisions. hESCs express high telomerase activity to sustain self-renewal and proliferation, and iPSCs also demonstrate high telomerase activity and express hTERT (human [telomerase reverse transcriptase](http://en.wikipedia.org/wiki/Telomerase_reverse_transcriptase)), a necessary component in the telomerase protein complex.
* Pluripotency: iPSCs were capable of differentiation in a fashion similar to ESCs into fully differentiated tissues.
	+ Neural differentiation: iPSCs were differentiated into [neurons](http://en.wikipedia.org/wiki/Neuron), expressing βIII-tubulin, tyrosine hydroxylase, AADC, DAT, ChAT, LMX1B, and MAP2. The presence of [catecholamine](http://en.wikipedia.org/wiki/Catecholamine)-associated enzymes may indicate that iPSCs, like hESCs, may be differentiable into [dopaminergic](http://en.wikipedia.org/wiki/Dopaminergic) neurons. Stem cell-associated genes were downregulated after differentiation.
	+ Cardiac differentiation: iPSCs were differentiated into [cardiomyocytes](http://en.wikipedia.org/wiki/Cardiac_muscle) that spontaneously began beating. Cardiomyocytes expressed TnTc, MEF2C, MYL2A, MYHCβ, and NKX2.5. Stem cell-associated genes were downregulated after differentiation.
	+ Teratoma formation: iPSCs injected into [immunodeficient](http://en.wikipedia.org/wiki/Immunodeficiency) mice spontaneously formed [teratomas](http://en.wikipedia.org/wiki/Teratoma) after nine weeks. Teratomas are tumors of multiple lineages containing tissue derived from the three [germ layers](http://en.wikipedia.org/wiki/Germ_layers) [endoderm](http://en.wikipedia.org/wiki/Endoderm), [mesoderm](http://en.wikipedia.org/wiki/Mesoderm) and [ectoderm](http://en.wikipedia.org/wiki/Ectoderm); this is unlike other tumors, which typically are of only one cell type. Teratoma formation is a landmark test for pluripotency.
	+ Embryoid body: hESCs in culture spontaneously form ball-like embryo-like structures termed "[embryoid bodies](http://en.wikipedia.org/wiki/Embryoid_body)", which consist of a core of mitotically active and differentiating hESCs and a periphery of fully differentiated cells from all three germ layers. iPSCs also form embryoid bodies and have peripheral differentiated cells.
	+ Chimeric mice: hESCs naturally reside within the inner cell mass ([embryoblast](http://en.wikipedia.org/wiki/Embryoblast)) of [blastocysts](http://en.wikipedia.org/wiki/Blastocyst), and in the embryoblast, differentiate into the embryo while the blastocyst’s shell ([trophoblast](http://en.wikipedia.org/wiki/Trophoblast)) differentiates into extraembryonic tissues. The hollow trophoblast is unable to form a living embryo, and thus it is necessary for the embryonic stem cells within the embryoblast to differentiate and form the embryo. iPSCs were injected by [micropipette](http://en.wikipedia.org/wiki/Micropipette) into a trophoblast, and the blastocyst was transferred to recipient females. [Chimeric](http://en.wikipedia.org/wiki/Chimera_%28genetics%29) living mouse pups were created: mice with iPSC derivatives incorporated all across their bodies with 10%–90% chimerism.
	+ [Tetraploid complementation](http://en.wikipedia.org/wiki/Tetraploid_complementation_assay): iPS cells from mouse fetal fibroblasts injected into tetraploid blastocysts (which themselves can only form extra-embryonic tissues) can form whole, non-chimeric, fertile mice, although with low success rate.[[46]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-46)[[47]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-47)[[48]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-48)
* Epigenetic reprogramming
	+ Promoter demethylation: Methylation is the transfer of a methyl group to a DNA base, typically the transfer of a methyl group to a cytosine molecule in a CpG site (adjacent cytosine/guanine sequence). Widespread methylation of a gene interferes with [expression](http://en.wikipedia.org/wiki/Gene_expression) by preventing the activity of expression proteins, or by recruiting enzymes that interfere with expression. Thus, methylation of a gene effectively silences it by preventing transcription. Promoters of pluripotency-associated genes, including Oct-3/4, Rex1, and Nanog, were demethylated in iPSCs, demonstrating their promoter activity and the active promotion and expression of pluripotency-associated genes in iPSCs.
	+ DNA methylation globally: Human iPS cells are highly similar to ES cells in their patterns of which [cytosines](http://en.wikipedia.org/wiki/Cytosine) are [methylated](http://en.wikipedia.org/wiki/DNA_methylation), more than to any other cell type. However, on the order of a thousand sites show differences in several iPS cell lines. Half of these resemble the somatic cell line the iPS cells were derived from, the rest are iPSC-specific. Tens of regions which are [megabases](http://en.wikipedia.org/wiki/Megabases) in size have also been found where iPS cells are not reprogrammed to the ES cell state.[[49]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-49)
	+ Histone demethylation: [Histones](http://en.wikipedia.org/wiki/Histone) are compacting proteins that are structurally localized to DNA sequences that can affect their activity through various chromatin-related modifications. H3 histones associated with Oct-3/4, Sox2, and Nanog were demethylated, indicating the expression of Oct-3/4, Sox2, and Nanog.

**Safety for regenerative medicine[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=16" \o "Edit section: Safety for regenerative medicine)]**

* The major concern with the potential clinical application of iPSCs is their propensity to form tumors.[[50]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-50) Much the same as ESC, iPSCs readily form [teratoma](http://en.wikipedia.org/wiki/Teratoma) when injected into immunodeficient mice. Teratoma formation is considered a major obstacle to stem-cell based regenerative medicine by the FDA.
* A more recent study on motor functional recovery after spinal cord injuries in mice showed that after human-induced pluripotent stem cells were transplanted into the mice, the cells differentiated into three neural lineages in the spinal cord. The cells stimulated regrowth of the damaged spinal cord, maintained myelination, and formed synapses. These positive outcomes were observed for over 112 days after the spinal cord injury, without tumor formation.[[51]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-51)
* Since iPSCs can only be produced with high efficiency at this time using modifications, they are generally predicted to be less safe and more tumorigenic than hESC. All the genes that have been shown to promote iPSC formation have also been linked to cancer in one way or another. Some of the genes are known oncogenes, including the members of the Myc family. While omitting Myc allows for IPSC formation, the efficiency is reduced up to 100 fold.
* A non-genetic method of producing iPSCs has been demonstrated using recombinant proteins, but its efficiency was quite low.[[5]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-urlGeneration_of_Induced_Pluripotent_Stem_Cells_Using_Recombinant_Proteins-5) However, refinements to this methodology yielding higher efficiency may lead to production of safer iPSCs. Other approaches such as using adenovirus or plasmids are generally thought to be safer than retroviral methods.
* An important area for future studies in the iPSC field is directly testing iPSC tumorigenicity using methods that mimic the approaches that would be used for regenerative medicine therapies. Such studies are crucial since iPSCs not only form teratoma, but also mice derived from iPSCs have a high incidence of death from malignant cancer.[[52]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-52) A recent paper came out in the journal Stem Cells indicating that iPS cells are far more tumorigenic than ESC, supporting the notion that iPS cell safety is a serious concern.[[53]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-53)
* Concern regarding the immunogenicity of IPS cells arose in 2011 when Zhou et al. performed a study involving a teratomaformation assay and demonstrated that IPS cells produced an immune response strong enough to cause rejection of the cells. When a similar procedure was performed on genetically equivalent ES cells however, Zhou et al. found [teratomas](http://en.wikipedia.org/wiki/Teratoma), which indicated that the cells were tolerated by the immune system.[[54]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-54) In 2013, Araki et al. attempted to reproduce the conclusion obtained by Zhou et al. using a different procedure. They took cells from a chimera that had been grown from IPSC clones and a mouse embryo, this tissue was then transplanted into [syngenic](http://en.wikipedia.org/wiki/Syngenic) mice. They conducted a similar trial using ES cells instead of IPSC clone and compared the results. Findings indicate that there was no significant difference in the immunogenic response produced by the IPS cells and the ES cells. Furthermore, Araki et al. reported little or no immunogenic response for both cell lines.[[55]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-55) Thus, Araki et al. was unable to come to the same conclusion as Zhou et al.

Recent achievements and future tasks for safe iPSC-based cell therapy are collected in the review of Okano et al.[[56]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-56)

**An open future[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=17" \o "Edit section: An open future)]**

The task of producing iPS cells continues to be challenging due to the six problems mentioned above. A key tradeoff to overcome is that between efficiency and genomic integration. Most methods that do not rely on the integration of transgenes are inefficient, while those that do rely on the integration of transgenes face the problems of incomplete reprogramming and tumor genesis, although a vast number of techniques and methods have been attempted. Another large set of strategies is to perform a proteomic characterization of iPS cells. The Wu group at [Stanford University](http://en.wikipedia.org/wiki/Stanford_University) has made significant progress with this strategy.[[57]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-57) Further studies and new strategies should generate optimal solutions to the five main challenges. One approach might attempt to combine the positive attributes of these strategies into an ultimately effective technique for reprogramming cells to iPS cells.

Another approach is the use of iPS cells derived from patients to identify therapeutic drugs able to rescue a phenotype. For instance, iPS cell lines derived from patients affected by ectodermal dysplasia syndrome (EEC), in which the [p63](http://en.wikipedia.org/wiki/TP63) gene is mutated, display abnormal epithelial commitment that could be partially rescued by a small compound[[58]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell%22%20%5Cl%20%22cite_note-58)

**Medical research[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=18" \o "Edit section: Medical research)]**

**Disease modeling and drug development[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=19" \o "Edit section: Disease modeling and drug development)]**

An attractive feature of human iPS cells is the ability to derive them from adult patients to study the cellular basis of human disease. Since iPS cells are self-renewing and pluripotent, they represent a theoretically unlimited source of patient-derived cells which can be turned into any type of cell in the body. This is particularly important because many other types of human cells derived from patients tend to stop growing after a few passages in laboratory culture. iPS cells have been generated for a wide variety of human genetic diseases, including common disorders such as Down syndrome and polycystic kidney disease.[[59]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-59)[[60]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-60) In many instances, the patient-derived iPS cells exhibit cellular defects not observed in iPS cells from healthy patients, providing insight into the pathophysiology of the disease.[[61]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-61) An international collaborated project, StemBANCC, was formed in 2012 to build a collection of iPS cell lines for drug screening for a variety of disease. Managed by the [University of Oxford](http://en.wikipedia.org/wiki/University_of_Oxford), the effort pooled funds and resources from 10 pharmaceutical companies and 23 universities. The goal is to generate a library of 1,500 iPS cell lines which will be used in early drug testing by providing a simulated human disease environment.[[62]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-62)

**Organ synthesis[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=20" \o "Edit section: Organ synthesis)]**

A proof-of-concept of using induced pluripotent stem cells (iPSCs) to generate human organ for [transplantation](http://en.wikipedia.org/wiki/Organ_transplant) was reported by researchers from Japan. Human ‘[liver](http://en.wikipedia.org/wiki/Liver) buds’ (iPSC-LBs) were grown from a mixture of three different kinds of stem cells: [hepatocytes](http://en.wikipedia.org/wiki/Hepatocytes) (for liver function) coaxed from iPSCs; [endothelial stem cells](http://en.wikipedia.org/wiki/Endothelial_stem_cells) (to form lining of [blood vessels](http://en.wikipedia.org/wiki/Blood_vessels)) from [umbilical cord blood](http://en.wikipedia.org/wiki/Umbilical_cord_blood); and [mesenchymal stem cells](http://en.wikipedia.org/wiki/Mesenchymal_stem_cells) (to form [connective tissue](http://en.wikipedia.org/wiki/Connective_tissue)). This new approach allows different cell types to self-organize into a complex organ, mimicking the process in [fetal development](http://en.wikipedia.org/wiki/Fetal_development). After growing *in vitro* for a few days, the liver buds were transplanted into mice where the ‘liver’ quickly connected with the host blood vessels and continued to grow. Most importantly, it performed regular liver functions including metabolizing drugs and producing liver-specific proteins. Further studies will monitor the longevity of the transplanted organ in the host body (ability to integrate or avoid [rejection](http://en.wikipedia.org/wiki/Transplant_rejection)) and whether it will transform into [tumors](http://en.wikipedia.org/wiki/Tumors).[[63]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-63)[[64]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-64) Using this method, cells from one mouse could be used to test 1,000 drug compounds to treat liver disease, and reduce animal use by up to 50,000.[[65]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-65)

**Tissue repair[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=21" \o "Edit section: Tissue repair)]**

Embryonic cord-blood cells were induced into pluripotent stem cells using plasmid DNA. Using cell surface endothelial/pericytic markers [CD31](http://en.wikipedia.org/wiki/CD31) and [CD146](http://en.wikipedia.org/wiki/CD146), researchers identified 'vascular progenitor', the high-quality, multipotent vascular stem cells. After the iPS cells were injected directly into the [vitreous](http://en.wikipedia.org/wiki/Vitreous_humour) of the damaged [retina](http://en.wikipedia.org/wiki/Retina) of mice, the stem cells engrafted into the retina, grew and repaired the [vascular vessels](http://en.wikipedia.org/wiki/Blood_vessel).[[66]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-66)[[67]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-67)

**Red blood cells[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=22" \o "Edit section: Red blood cells)]**

In 2014, [type O](http://en.wikipedia.org/wiki/Type_O) [red blood cells](http://en.wikipedia.org/wiki/Red_blood_cell) were synthesized at the Scottish National Blood Transfusion Service from iPSC. The cells were induced to become a [mesoderm](http://en.wikipedia.org/wiki/Mesoderm) and then [blood cells](http://en.wikipedia.org/wiki/Blood_cell) and then red blood cells. The final step was to make them eject their nuclei and mature properly. Type O can be transfused into all patients. Each pint of blood contains about two trillion red blood cells, while some 107 million blood donations are collected globally every year. Human transfusions were not expected to begin until 2016.[[68]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-68)

**Clinical trial[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=23" \o "Edit section: Clinical trial)]**

The first human [clinical trial](http://en.wikipedia.org/wiki/Clinical_trial) using [autologous](http://en.wikipedia.org/wiki/Autologous) iPSCs is approved by the [Japan Ministry Health](http://en.wikipedia.org/wiki/Japan_Ministry_Health) and will be conducted in 2014 in [Kobe](http://en.wikipedia.org/wiki/Kobe). iPSCs derived from skin cells from six patients suffering from [wet age-related macular degeneration](http://en.wikipedia.org/wiki/Macular_degeneration#wet_AMD) will be reprogrammed to differentiate into [retinal pigment epithelial (RPE) cells](http://en.wikipedia.org/wiki/Retinal_pigment_epithelium). The cell sheet will be transplanted into the affected [retina](http://en.wikipedia.org/wiki/Retina) where the degenerated RPE tissue has been excised. Safety and vision restoration monitoring is expected to last one to three years.[[69]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-69)[[70]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-rikentrial-70) The benefits of using autologous iPSCs are that there is theoretically no risk of [rejection](http://en.wikipedia.org/wiki/Transplant_rejection) and it eliminates the need to use [embryonic stem cells](http://en.wikipedia.org/wiki/Embryonic_stem_cells).[[70]](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_note-rikentrial-70)

**See also[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=24" \o "Edit section: See also)]**

* [Induced stem cells](http://en.wikipedia.org/wiki/Induced_stem_cells)
* [Stem cell treatments](http://en.wikipedia.org/wiki/Stem_cell_treatments)
* [Stimulus-triggered acquisition of pluripotency cell](http://en.wikipedia.org/wiki/Stimulus-triggered_acquisition_of_pluripotency_cell), a type of pluripotent stem cell that can be generated by immersing cells in an acid
* [Induced pluripotent stem cells vs embryonic stem cells lines obtained by SCNT (discussion)](http://en.wikiversity.org/wiki/Talk%3AInduced_stem_cells#Induced_stem_cells_vs_embryonic_stem_cells_lines_obtained_by_SCNT_.28discussion.29)

**References[[edit](http://en.wikipedia.org/w/index.php?title=Induced_pluripotent_stem_cell&action=edit&section=25" \o "Edit section: References)]**

* 1. ^ [***a***](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-ReferenceA_1-0) [***b***](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-ReferenceA_1-1) [***c***](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-ReferenceA_1-2) [***d***](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-ReferenceA_1-3) Takahashi, K; Yamanaka, S (2006). "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors". *Cell* **126** (4): 663–76. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1016/j.cell.2006.07.024](http://dx.doi.org/10.1016/j.cell.2006.07.024). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [16904174](http://www.ncbi.nlm.nih.gov/pubmed/16904174).
	2. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-2) ["The Nobel Prize in Physiology or Medicine – 2012 Press Release"](http://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/press.html). Nobel Media AB. 8 October 2012.
	3. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-3) Klimanskaya et al (2006). ["Human embryonic stem cell lines derived from single blastomeres"](http://www.nature.com/nature/journal/v444/n7118/abs/nature05142.html). *Nature* (Nature) **444**: 484–485. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature05142](http://dx.doi.org/10.1038/nature05142). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [16929302](http://www.ncbi.nlm.nih.gov/pubmed/16929302).
	4. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-urlCancer_threat_removed_from_stem_cells.2C_scientists_say_-_Los_Angeles_Times_4-0) Kaplan, Karen (2009-03-06). ["Cancer threat removed from stem cells, scientists say"](http://www.latimes.com/news/nationworld/nation/la-sci-stemcell6-2009mar06%2C0%2C63456.story). *Los Angeles Times*.
	5. ^ [***a***](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-urlGeneration_of_Induced_Pluripotent_Stem_Cells_Using_Recombinant_Proteins_5-0) [***b***](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-urlGeneration_of_Induced_Pluripotent_Stem_Cells_Using_Recombinant_Proteins_5-1) Zhou H, Wu S, Joo JY, et al. (May 2009). ["Generation of Induced Pluripotent Stem Cells Using Recombinant Proteins"](http://www.cell.com/cell-stem-cell/fulltext/S1934-5909%2809%2900159-3). *Cell Stem Cell* **4** (5): 381–4. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1016/j.stem.2009.04.005](http://dx.doi.org/10.1016/j.stem.2009.04.005). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [19398399](http://www.ncbi.nlm.nih.gov/pubmed/19398399). Retrieved April 23, 2009.
	6. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-6) Okita, K; Ichisaka, T; Yamanaka, S (2007). "Generation of germline-competent induced pluripotent stem cells". *Nature* **448** (7151): 313–7. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature05934](http://dx.doi.org/10.1038/nature05934). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [17554338](http://www.ncbi.nlm.nih.gov/pubmed/17554338).
	7. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-7) Wernig, M; Meissner, A; Foreman, R; Brambrink, T; Ku, M; Hochedlinger, K; Bernstein, BE; Jaenisch, R (2007). "In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state". *Nature* **448** (7151): 318–24. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature05944](http://dx.doi.org/10.1038/nature05944). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [17554336](http://www.ncbi.nlm.nih.gov/pubmed/17554336).
	8. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-8) Maherali N, et al. (2007). "Directly reprogrammed fibroblasts show global epigenetic remodeling and widespread tissue contribution". *Cell Stem Cell* **1** (1): 55–70. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1016/j.stem.2007.05.014](http://dx.doi.org/10.1016/j.stem.2007.05.014). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [18371336](http://www.ncbi.nlm.nih.gov/pubmed/18371336).
	9. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-9) [Generations of iPSCs and related references](http://sbaminbeta.blogspot.com/2007/08/reprogramming-cell-part-4-ips.html)
	10. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-swaminathan_10-0) Swaminathan, Nikhil (2007-11-30). ["Stem Cells – This Time Without the Cancer"](http://www.sciam.com/article.cfm?id=stem-cells-without-cancer). *Scientific American News*. Retrieved 2007-12-11.
	11. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-11) Moad, Mohammad; Pal, Deepali; Hepburn, Anastasia C; Williamson, Stuart C; Wilson, Laura; Lako, Majlinda; Armstrong, Lyle; Hayward, Simon W; Franco, Omar E; Cates, Justin M; Fordham, Sarah E; Przyborski, Stefan; Carr-Wilkinson, Jane; Robson, Craig N; Heer, Rakesh (2013). "A Novel Model of Urinary Tract Differentiation, Tissue Regeneration, and Disease: Reprogramming Human Prostate and Bladder Cells into Induced Pluripotent Stem Cells.". *European Urology* **64** (5): 753–761. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1016/j.eururo.2013.03.054](http://dx.doi.org/10.1016/j.eururo.2013.03.054). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [23582880](http://www.ncbi.nlm.nih.gov/pubmed/23582880).  Cite uses deprecated parameters ([help](http://en.wikipedia.org/wiki/Help%3ACS1_errors#deprecated_params))
	12. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-slasdot_12-0) ["Scientists Create Mice From 2 Fathers"](http://science.slashdot.org/article.pl?sid=10/12/09/0345214). *Slashdot*. 2010-12-08. Retrieved 2010-12-10.
	13. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-bioreprod_13-0) Deng, JM; Satoh, K; Wang, H; Chang, H; Zhang, Z; Stewart, MD; Cooney, AJ; Behringer, RR (2010-12-08). ["Generation of Viable Male and Female Mice from Two Fathers"](http://www.biolreprod.org/content/early/2010/12/07/biolreprod.110.088831.abstract?sid=a58c9766-5f37-4d99-a02b-8ad9bdeeecb1). *Biology of Reproduction* **84** (3): 613–8. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1095/biolreprod.110.088831](http://dx.doi.org/10.1095/biolreprod.110.088831). [PMC](http://en.wikipedia.org/wiki/PubMed_Central) [3043133](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3043133). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [21148107](http://www.ncbi.nlm.nih.gov/pubmed/21148107).
	14. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-mdaily_14-0) ["Reproductive scientists create mice from 2 fathers"](http://www.medicaldaily.com/news/20101208/4511/reproductive-scientists-create-mice-from-2-fathers.htm). *Medical Daily*. 2010-12-08. Retrieved 2010-12-09.
	15. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-nature_15-0) Baker, Monya (2007-12-06). ["Adult cells reprogrammed to pluripotency, without tumors"](http://www.nature.com/stemcells/2007/0712/071206/full/stemcells.2007.124.html). *Nature Reports Stem Cells*. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/stemcells.2007.124](http://dx.doi.org/10.1038/stemcells.2007.124). Retrieved 2007-12-11.
	16. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-16) Kolata, Gina (2007-11-21). ["Scientists Bypass Need for Embryo to Get Stem Cells"](http://www.nytimes.com/2007/11/21/science/21stem.html). *The New York Times*. [ISSN](http://en.wikipedia.org/wiki/International_Standard_Serial_Number) [0362-4331](http://www.worldcat.org/issn/0362-4331). Retrieved 2007-12-11.
	17. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-17) Yu J, Vodyanik MA, et al. (2007). "Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells". [*Science*](http://en.wikipedia.org/wiki/Science_%28journal%29) **318** (5858): 1917–1920. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1126/science.1151526](http://dx.doi.org/10.1126/science.1151526). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [18029452](http://www.ncbi.nlm.nih.gov/pubmed/18029452).
	18. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-18) Takahashi K, et al. (2007). "Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors". *Cell* **131** (5): 861–872. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1016/j.cell.2007.11.019](http://dx.doi.org/10.1016/j.cell.2007.11.019). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [18035408](http://www.ncbi.nlm.nih.gov/pubmed/18035408).
	19. ^ [***a***](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-urinecell_19-0) [***b***](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-urinecell_19-1) Zhou, Ting; Benda, Christina; Dunzinger, Sarah; Huang, Yinghua; Ho, Jenny Cy; Yang, Jiayin; Wang, Yu; Zhang, Ya; Zhuang, Qiang; Li, Yanhua; Bao, Xichen; Tse, Hung-Fat; Grillari, Johannes; Grillari-Voglauer, Regina; Pei, Duanqing; Esteban, Miguel A (7 November 2012). ["Generation of human induced pluripotent stem cells from urine samples"](http://www.nature.com/nprot/journal/v7/n12/full/nprot.2012.115.html). *Nature Protocols* **7** (12): 2080–2089. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nprot.2012.115](http://dx.doi.org/10.1038/nprot.2012.115). Retrieved 1 December 2012.  Cite uses deprecated parameters ([help](http://en.wikipedia.org/wiki/Help%3ACS1_errors#deprecated_params))
	20. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-20) Luo, M., et al & Tao, W., Lu, Z., Grummt, I. (2013), NuRD Blocks Reprogramming of Mouse Somatic Cells into Pluripotent Stem Cells. STEM CELLS, 31: 1278–1286. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1002/stem.1374](http://dx.doi.org/10.1002/stem.1374)
	21. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-21) Yoach Rais, Asaf Zviran, Shay Geula, et al. (2013) Deterministic direct reprogramming of somatic cells to pluripotency. Nature, [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature12587](http://dx.doi.org/10.1038/nature12587)
	22. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-Switching_cell_fate_22-0) Selvaraj V, Plane JM, Williams AJ, Deng W (April 2010). ["Switching cell fate: the remarkable rise of induced pluripotent stem cells and lineage reprogramming technologies"](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2843790). *Trends in Biotechnology* **28** (4): 214–23. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1016/j.tibtech.2010.01.002](http://dx.doi.org/10.1016/j.tibtech.2010.01.002). [PMC](http://en.wikipedia.org/wiki/PubMed_Central) [2843790](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2843790). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [20149468](http://www.ncbi.nlm.nih.gov/pubmed/20149468).
	23. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-23) Okita, K; Nakagawa, M.; Hyenjong, H.; Ichisaka, T.; Yamanaka, S. (2008). "Generation of mouse induced pluripotent stem cells without viral vectors". *Science* **322** (5903): 949–953. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1126/science.1164270](http://dx.doi.org/10.1126/science.1164270). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [18845712](http://www.ncbi.nlm.nih.gov/pubmed/18845712).
	24. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-24) Stadtfeld, M; Nakagawa, M; Hyenjong, H; Ichisaka, T; Yamanaka, S (2008). "Induced pluripotent stem cells generated without viral integration". *Science* **322** (5903): 949–53. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1126/science.1164270](http://dx.doi.org/10.1126/science.1164270). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [18845712](http://www.ncbi.nlm.nih.gov/pubmed/18845712).
	25. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-25) Woltjen, K; Michael, IP; Mohseni, P; Desai, R; Mileikovsky, M; Hämäläinen, R; Cowling, R; Wang, W; Liu, P (2009). "piggyBac transposition reprograms fibroblasts to induced pluripotent stem cells". *Nature* **458** (7239): 766–770. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature07863](http://dx.doi.org/10.1038/nature07863). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [19252478](http://www.ncbi.nlm.nih.gov/pubmed/19252478).
	26. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-26) RM, Mario; Strati, Katerina; Li, Han; Murga, Matilde; Blanco, Raquel; Ortega, Sagrario; Fernandez-Capetillo, Oscar; Serrano, Manuel; Blasco, Maria A. (2009). "A p53-mediated DNA damage response limits reprogramming to ensure iPS cell genomic integrity". *Nature* **460** (7259): 1149–1153. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature08287](http://dx.doi.org/10.1038/nature08287). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [19668189](http://www.ncbi.nlm.nih.gov/pubmed/19668189).
	27. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-27) Zhao, XY; Li, Wei; Lv, Zhuo; Liu, Lei; Tong, Man; Hai, Tang; Hao, Jie; Guo, Chang-Long; Ma, Qing-wen (2009). "iPS cells produce viable mice through tetraploid complementation". *Nature* **461** (7260): 86–90. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature08267](http://dx.doi.org/10.1038/nature08267). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [19672241](http://www.ncbi.nlm.nih.gov/pubmed/19672241).
	28. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-28) Huangfu D, Maehr R, Guo W, et al. (2008). "Induction of pluripotent stem cells by defined factors is greatly improved by small-molecule compounds". *Nat Biotechnol* **26** (7): 795–7. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nbt1418](http://dx.doi.org/10.1038/nbt1418). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [18568017](http://www.ncbi.nlm.nih.gov/pubmed/18568017).
	29. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-29) Desponts, Shi; Desponts, Caroline; Do, Jeong Tae; Hahm, Heung Sik; Schöler, Hans R.; Ding, Sheng (November 2008). "Induction of pluripotent stem cells from mouse embryonic fibroblasts by Oct4 and Klf4 with small-molecule compounds". *Cell Stem Cell* **3** (5): 568–74. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1016/j.stem.2008.10.004](http://dx.doi.org/10.1016/j.stem.2008.10.004). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [18983970](http://www.ncbi.nlm.nih.gov/pubmed/18983970).
	30. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-30) Cyranoski, David (18 July 2013). ["Stem cells reprogrammed using chemicals alone"](http://www.nature.com/news/stem-cells-reprogrammed-using-chemicals-alone-1.13416). Nature.com. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature.2013.13416](http://dx.doi.org/10.1038/nature.2013.13416). Retrieved 22 July 2013.
	31. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-31) Deng, Hongkui; Hou, Pingping; Li, Yanqin; Zhang, Xu; Liu, Chun; Guan, Jingyang; Li, Honggang; Zhao, Ting; Ye, Junqing (18 July 2013). "Pluripotent Stem Cells Induced from Mouse Somatic Cells by Small-Molecule Compounds". *Science* (sciencemag.org). [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1126/science.1239278](http://dx.doi.org/10.1126/science.1239278).
	32. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-name_32-0) ["Major Step In Making Better Stem Cells From Adult Tissue"](http://www.sciencedaily.com/releases/2009/10/091018141615.htm). *Science Daily*. 19 October 2009. Retrieved 30 September 2013.
	33. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-33) Ding, Sheng; Lin, Tongxiang; Ambasudhan, Rajesh; Yuan, Xu; Li, Wenlin; Hilcove, Ramzey; Lin, Xiangyi; Hahm, Heung (2009). "A chemical platform for improved induction of human iPSCs". *Nature Methods* (Nature) **6**: 805–808. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nmeth.1393](http://dx.doi.org/10.1038/nmeth.1393).
	34. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-34) Desponts, Shi; Desponts, Caroline; Do, Jeong Tae; Hahm, Heung Sik; Schöler, Hans R.; Ding, Sheng (2008). "Induction of pluripotent stem cells from mouse embryonic fibroblasts by Oct4 and Klf4 with small-molecule compounds". *Cell Stem Cell* **3** (5): 568–74. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1016/j.stem.2008.10.004](http://dx.doi.org/10.1016/j.stem.2008.10.004). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [18983970](http://www.ncbi.nlm.nih.gov/pubmed/18983970).
	35. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-35) Zhou, Wi; Freed, Curt R. (2009). "Adenoviral gene delivery can reprogram human fibroblasts to induced pluripotent stem cells". *Stem Cells* **27** (11): 2667–74. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1002/stem.201](http://dx.doi.org/10.1002/stem.201). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [19697349](http://www.ncbi.nlm.nih.gov/pubmed/19697349).
	36. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-36) Yamanaka, K.; Nakagawa, M.; Hyenjong, H.; Ichisaka, T.; Yamanaka, S. (2008). "Generation of Mouse Induced Pluripotent Stem Cells Without Viral Vectors". *Science* **322** (5903): 949–53. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1126/science.1164270](http://dx.doi.org/10.1126/science.1164270). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [18845712](http://www.ncbi.nlm.nih.gov/pubmed/18845712).
	37. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-37) David Cyranoski for Nature News. January 29, 2014 [Acid bath offers easy path to stem cells](http://www.nature.com/news/acid-bath-offers-easy-path-to-stem-cells-1.14600)
	38. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-38) Tracy Vence for the Scientist. March 11, 2014 [Call for STAP Retractions](http://www.the-scientist.com/?articles.view/articleNo/39397/title/Call-for-STAP-Retractions/)
	39. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-retract_39-0) Elaine Lies (4 June 2014). ["Japan researcher agrees to withdraw disputed stem cell paper"](http://www.reuters.com/article/2014/06/04/us-japan-stemcells-researcher-idUSKBN0EF0SO20140604). *Reuters*. Retrieved 4 June 2014.
	40. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-40) Press Release (1 April 2014). ["Report on STAP Cell Research Paper Investigation"](http://www.riken.jp/en/pr/press/2014/20140401_2/). RIKEN. Retrieved 2 June 2014.
	41. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-41) Judson, RL. "Embryonic stem cell-specific microRNAs promote induced pluripotency". *Source the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, University of California, San Francisco, San Francisco, California, USA*.
	42. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-42) Xichen Bao, Xihua Zhu, Baojian Liao, et al & Miguel A Esteban (2013) MicroRNAs in somatic cell reprogramming. Current Opinion in Cell Biology 25(2), 208–214 <http://dx.doi.org/10.1016/j.ceb.2012.12.004>
	43. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-Maekawa_M_et_al_43-0) Maekawa M et al (2011). "Direct reprogramming of somatic cells is promoted by maternal transcription factor Glis1". [*Nature*](http://en.wikipedia.org/wiki/Nature_%28journal%29) **474**: 225–229. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature10106](http://dx.doi.org/10.1038/nature10106). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [21654807](http://www.ncbi.nlm.nih.gov/pubmed/21654807).
	44. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-cell.com_44-0) Takahashi K, Yamanaka S (August 2006). ["Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors"](http://www.cell.com/abstract/S0092-8674%2806%2900976-7). *Cell* **126** (4): 663–76. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1016/j.cell.2006.07.024](http://dx.doi.org/10.1016/j.cell.2006.07.024). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [16904174](http://www.ncbi.nlm.nih.gov/pubmed/16904174).
	45. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-45) Young, D. (2010). ["Chromatin structure and gene expression programs of human embryonic and induced pluripotent stem cells."](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3010384/). *Cell Stem Cell* **7** (?): 249–257. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1016/j.stem.2010.06.015](http://dx.doi.org/10.1016/j.stem.2010.06.015). [PMC](http://en.wikipedia.org/wiki/PubMed_Central) [3010384](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3010384). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [20682450](http://www.ncbi.nlm.nih.gov/pubmed/20682450).
	46. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-46) Zhao, Xiao-Yang; Li, Wei; Lv, Zhuo; Liu, Lei; Tong, Man; Hai, Tang; Hao, Jie; Guo, Chang-Long; Ma, Qing-wen (2009). "iPS cells produce viable mice through tetraploid complementation". [*Nature*](http://en.wikipedia.org/wiki/Nature_%28journal%29) **461** (7260): 86–90. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature08267](http://dx.doi.org/10.1038/nature08267). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [19672241](http://www.ncbi.nlm.nih.gov/pubmed/19672241).
	47. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-47) Kang, Lan; Wang, Jianle; Zhang, Yu; Kou, Zhaohui; Gao, Shaorong (2009). "iPS Cells Can Support Full-Term Development of Tetraploid Blastocyst-Complemented Embryos". *Cell Stem Cell* **5** (2): 135–138. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1016/j.stem.2009.07.001](http://dx.doi.org/10.1016/j.stem.2009.07.001). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [19631602](http://www.ncbi.nlm.nih.gov/pubmed/19631602).
	48. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-48) Michael J. Boland et al. (2009). "Adult mice generated from induced pluripotent stem cells". [*Nature*](http://en.wikipedia.org/wiki/Nature_%28journal%29) **461** (7260): 91–4. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature08310](http://dx.doi.org/10.1038/nature08310). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [19672243](http://www.ncbi.nlm.nih.gov/pubmed/19672243).
	49. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-49) Lister R, Pelizzola M, Kida YS, Hawkins D, Nery JR et al. (2011). ["Hotspots of aberrant epigenomic reprogramming in human induced pluripotent stem cells"](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3100360). *Nature* **471** (7336): 68–73. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature09798](http://dx.doi.org/10.1038/nature09798). [PMC](http://en.wikipedia.org/wiki/PubMed_Central) [3100360](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3100360). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [21289626](http://www.ncbi.nlm.nih.gov/pubmed/21289626).
	50. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-50) Knoepfler, Paul S. (2009). ["Deconstructing Stem Cell Tumorigenicity: A Roadmap to Safe Regenerative Medicine"](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2733374). *Stem Cells* **27** (5): 1050–1056. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1002/stem.37](http://dx.doi.org/10.1002/stem.37). [PMC](http://en.wikipedia.org/wiki/PubMed_Central) [2733374](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2733374). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [19415771](http://www.ncbi.nlm.nih.gov/pubmed/19415771).
	51. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-51) Satoshi, Nori (2011). ["Grafted Human-induced Pluripotent Stem-Cell–Derived Neurospheres Promote Motor Functional Recovery After Spinal Cord Injury In Mice"](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3189018). *PNAS* **108** (40): 16825–16830. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1073/pnas.1108077108](http://dx.doi.org/10.1073/pnas.1108077108). [PMC](http://en.wikipedia.org/wiki/PubMed_Central) [3189018](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3189018).
	52. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-52) Aoi, T.; Yae, K.; Nakagawa, M.; Ichisaka, T.; Okita, K.; Takahashi, K.; Chiba, T.; Yamanaka, S. (2008). "Generation of Pluripotent Stem Cells from Adult Mouse Liver and Stomach Cells". *Science* **321** (5889): 699–702. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1126/science.1154884](http://dx.doi.org/10.1126/science.1154884). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [18276851](http://www.ncbi.nlm.nih.gov/pubmed/18276851).
	53. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-53) Ivan Gutierrez-Aranda, "et al". (2010). ["Human Induced Pluripotent Stem Cells Develop Teratoma More Efficiently and Faster than Human Embryonic Stem Cells Regardless of the Site of Injection"](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2996086). *Stem Cells* **28** (9): 1568–1570. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1002/stem.471](http://dx.doi.org/10.1002/stem.471). [PMC](http://en.wikipedia.org/wiki/PubMed_Central) [2996086](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2996086). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [20641038](http://www.ncbi.nlm.nih.gov/pubmed/20641038).
	54. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-54) Zhao, Tongbiao; Zhen-Ning, Zhang,Zhili Rong, Yang Xu (13 May 2011). "Immunogenicity of induced pluripotent stem cells". *Nature* **474**: 212–215. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature10135](http://dx.doi.org/10.1038/nature10135). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [21572395](http://www.ncbi.nlm.nih.gov/pubmed/21572395).  Cite uses deprecated parameters ([help](http://en.wikipedia.org/wiki/Help%3ACS1_errors#deprecated_params)); |accessdate= requires |url= ([help](http://en.wikipedia.org/wiki/Help%3ACS1_errors#accessdate_missing_url))
	55. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-55) Araki, Ryoko; Mashiro Uda, Yuko Hoki, Misato Sunayama, Miki Nakamura, Shunsuke Ando, Mayumi Sugiura, Hisashi Ideno, Akemi Shimada, Akira Nifuji, Masume Abe (7 February 2013). "Negligible immunogenicity of terminally differentiated cells derived from induced pluripotent or embroyonic stem cells". *Nature* (494): 100–106. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature11807](http://dx.doi.org/10.1038/nature11807).  Cite uses deprecated parameters ([help](http://en.wikipedia.org/wiki/Help%3ACS1_errors#deprecated_params)); |accessdate= requires |url= ([help](http://en.wikipedia.org/wiki/Help%3ACS1_errors#accessdate_missing_url))
	56. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-56) Okano Hideyuki, Nakamura Masaya, Yoshida Kenji et al. "& Kyoko Miura (2013) Steps Toward Safe Cell Therapy Using Induced Pluripotent Stem Cells". *Circulation Research* **112**: 523–533. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1161/CIRCRESAHA.111.256149](http://dx.doi.org/10.1161/CIRCRESAHA.111.256149).
	57. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-57) Boland, MY; Hazen, Jennifer L.; Nazor, Kristopher L.; Rodriguez, Alberto R.; Gifford, Wesley; Martin, Greg; Kupriyanov, Sergey; Baldwin, Kristin K. (2009). "Adult mice generated from induced pluripotent stem cells". *Nature* **461** (7260): 91–4. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature08310](http://dx.doi.org/10.1038/nature08310). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [19672243](http://www.ncbi.nlm.nih.gov/pubmed/19672243).
	58. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-58) Shalom-Feuerstein R et al. Impaired epithelial differentiation of induced pluripotent stem cells from EEC patients is rescued by APR-246/PRIMA-1MET. P.N.A.S. 2012 <http://minus.com/lbmC3TVGDx350s>
	59. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-59) Park, IH; Arora, N; Huo, H; Maherali, N; Ahfeldt, T; Shimamura, A; Lensch, MW; Cowan, C; Hochedlinger, K; Daley, GQ (Sep 5, 2008). ["Disease-specific induced pluripotent stem cells."](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2633781). *Cell* **134** (5): 877–86. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1016/j.cell.2008.07.041](http://dx.doi.org/10.1016/j.cell.2008.07.041). [PMC](http://en.wikipedia.org/wiki/PubMed_Central) [2633781](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2633781). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [18691744](http://www.ncbi.nlm.nih.gov/pubmed/18691744).
	60. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-60) Freedman, BS; Lam, AQ; Sundsbak, JL; Iatrino, R; Su, X; Koon, SJ; Wu, M; Daheron, L; Harris, PC; Zhou, J; Bonventre, JV (October 2013). "Reduced ciliary polycystin-2 in induced pluripotent stem cells from polycystic kidney disease patients with PKD1 mutations.". *Journal of the American Society of Nephrology : JASN* **24** (10): 1571–86. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1681/ASN.2012111089](http://dx.doi.org/10.1681/ASN.2012111089). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [24009235](http://www.ncbi.nlm.nih.gov/pubmed/24009235).  Cite uses deprecated parameters ([help](http://en.wikipedia.org/wiki/Help%3ACS1_errors#deprecated_params))
	61. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-61) Grskovic, M; Javaherian, A; Strulovici, B; Daley, GQ (Nov 11, 2011). "Induced pluripotent stem cells--opportunities for disease modelling and drug discovery.". *Nature reviews. Drug discovery* **10** (12): 915–29. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nrd3577](http://dx.doi.org/10.1038/nrd3577). [PMID](http://en.wikipedia.org/wiki/PubMed_Identifier) [22076509](http://www.ncbi.nlm.nih.gov/pubmed/22076509).
	62. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-62) Gerlin, Andrea (5 December 2012). ["Roche, Pfizer, Sanofi Plan $72.7 Million Stem-Cell Bank"](http://www.bloomberg.com/news/2012-12-05/roche-pfizer-sanofi-plan-72-7-million-stem-cell-bank.html). Bloomberg.com. Retrieved 23 December 2012.
	63. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-63) Baker, Monya (3 July 2013). ["Miniature human liver grown in mice"](http://www.nature.com/news/miniature-human-liver-grown-in-mice-1.13324). Nature.com. Retrieved 19 July 2013.
	64. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-64) Takebe, Takanori; Sekine, Keisuke; Enomura, Masahiro; Koike, Hiroyuki; Kimura, Masaki; Ogaeri, Takurnori; Zhang, Ran-Ran; Ueno, Yasuharu; Zheng, Yun-Wen (3 July 2013). "Vascularized and functional human liver from an iPSC-derived organ bud transplant". *Nature.com* ([Nature](http://en.wikipedia.org/wiki/Nature_%28journal%29)). [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1038/nature12271](http://dx.doi.org/10.1038/nature12271).
	65. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-65) [Mini-Livers May Reduce Animal Testing](http://www.laboratoryequipment.com/videos/2014/02/mini-livers-may-reduce-animal-testing)
	66. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-66) Mullin, Emily (28 January 2014). ["Researchers repair retinas in mice with virus-free stem cells"](http://www.fiercebiotechresearch.com/story/researchers-repair-retinas-mice-virus-free-stem-cells/2014-01-28). fiercebiotech.com. Retrieved 17 February 2014.
	67. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-67) Zambidis, Elias; Lutty, Gerard; Park, Tea Soon; Bhutto, Imran et al. (2014). ["Vascular Progenitors From Cord Blood-Derived Induced Pluripotent Stem Cells Possess Augmented Capacity for Regenerating Ischemic Retinal Vasculature"](http://circ.ahajournals.org/content/129/3/359). *Circulation* (American Heart Association) **129**: 359–372. [doi](http://en.wikipedia.org/wiki/Digital_object_identifier):[10.1161/CIRCULATIONAHA.113.003000](http://dx.doi.org/10.1161/CIRCULATIONAHA.113.003000).
	68. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-68) ["First transfusions of "manufactured" blood planned for 2016"](http://www.gizmag.com/lab-grown-red-blood-cells/31745/). Gizmag.com. Retrieved 2014-04-23.
	69. [**^**](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-69) Riken Center for Developmental Biology. ["Information on proposed pilot study of the safety and feasibility of transplantation of autologous hiPSC-derived retinal pigment epithelium (RPE) cell sheets in patients with neovascular age-related macular degeneration"](http://www.cdb.riken.jp/en/02_research/0208_regenerative01.html). Retrieved 23 July 2013.
	70. ^ [***a***](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-rikentrial_70-0) [***b***](http://en.wikipedia.org/wiki/Induced_pluripotent_stem_cell#cite_ref-rikentrial_70-1) Gallagher, James (19 July 2013). ["Pioneering adult stem cell trial approved by Japan"](http://www.bbc.co.uk/news/health-23374622). [*BBC News*](http://en.wikipedia.org/wiki/BBC_News). Retrieved 23 July 2013