

NEWS

Simple switch turns cells embryonic

Research reported this week by three different groups shows that normal skin cells can be reprogrammed to an embryonic state in mice¹⁻³. The race is now on to apply the surprisingly straightforward procedure to human cells.

If researchers succeed, it will make it relatively easy to produce cells that seem indistinguishable from embryonic stem cells, and that are genetically matched to individual patients. There are limits to how useful and safe these would be for therapeutic use in the near term, but they should quickly prove a boon in the lab.

"It would change the way we see things quite dramatically," says Alan Trounson of Monash University in Victoria, Australia. Trounson wasn't involved in the new work but says he plans to start using the technique "tomorrow". "I can think of a dozen experiments right now — and they're all good ones," he says.

In theory, embryonic stem cells can propagate themselves indefinitely and are able to become any type of cell in the body. But so far, the only way to obtain embryonic stem cells involves destroying an embryo, and to get a genetic match for a patient would mean, in effect, cloning that person — all of which raise difficult ethical questions.

As well as having potential ethical difficulties, the 'cloning' procedure is technically difficult. It involves obtaining unfertilized eggs, replacing their genetic material with that from

an adult cell and then forcing the cell to divide to create an early-stage embryo, from which the stem cells can be harvested. Those barriers may have now been broken down.

"Neither eggs nor embryos are necessary. I've never worked with either," says Shinya Yamanaka of Kyoto University, who has pioneered the new technique.

Last year, Yamanaka introduced a system that uses mouse fibroblasts, a common cell type that can easily be harvested from skin, instead of eggs⁴. Four genes, which code for four specific proteins known as transcription factors, are transferred into the cells using retroviruses. The proteins trigger the expression of other genes that lead the cells to become pluripotent, meaning that they could potentially become any of the body's cells. Yamanaka calls them induced pluripotent stem cells (iPS cells). "It's easy. There's no trick, no magic," says Yamanaka.

The results were met with amazement, along with a good dose of scepticism. Four factors seemed too simple. And although the cells had some characteristics of embryonic cells — they formed colonies, could propagate continuously and could form cancerous growths called teratomas — they lacked others. Introduction of iPS cells into a developing embryo, for example, did not produce a 'chimaera' — a mouse carrying a mix of DNA from both the original embryo and the iPS cells throughout its body. "I

was not comfortable with the term 'pluripotent' last year," says Hans Schöler, a stem-cell specialist at the Max Planck Institute for Molecular Biomedicine in Münster who is not involved with any of the three articles.

This week, Yamanaka presents a second generation of iPS cells¹, which pass all these tests. In addition, a group led by Rudolf Jaenisch² at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, and a collaborative effort³ between Konrad Hochedlinger of the Harvard Stem Cell Institute and Kathrin Plath of the University of California, Los Angeles, used the same four factors and got strikingly similar results.

"It's a relief as some people questioned our results, especially after the Hwang scandal," says Yamanaka, referring to the irreproducible cloning work of Woo Suk Hwang, which turned out to be fraudulent. Schöler agrees: "Now we can be confident that this is something worth building on."

The improvement over last year's results was simple. The four transcription factors used by Yamanaka reprogramme cells inconsistently and inefficiently, so that less than 0.1% of the million cells in a simple skin biopsy will be fully reprogrammed. The difficulty is isolating those in which reprogramming has been successful. Researchers do this by inserting a gene for antibiotic resistance that is activated only when proteins characteristic of stem cells are expressed. The cells can then be doused with

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Bush's climate plan 'nothing new'

President George W. Bush's 31 May announcement of a "new framework" for international efforts to confront climate change sounded, at first, like a sharp turnaround by the White House. But as analysts dissected his statements, many concluded that he had said little new.

In a speech in Washington DC to the Global Leadership Campaign, a group that lobbies for greater spending on international affairs, Bush called for the top-emitting countries to meet by the end of 2008 to set a long-term global goal for greenhouse-gas emissions. The notion of Bush proposing a global

target to tackle climate change caused a flurry of excitement.

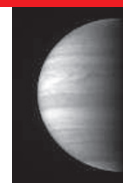
But in a briefing afterwards, James Connaughton, the president's environmental adviser, said that Bush was referring only to "a long-term aspirational goal" rather than a binding commitment. "It is the implementing mechanisms that become binding," he said.

"It remains to be seen whether this initiative means anything," says Bert Metz, a climatologist at the Netherlands Environmental Assessment Agency in Bilthoven. Stabilizing atmospheric levels of greenhouse gases, he says, requires "ambitious and urgent international



Leadership talk: George Bush hints at setting global targets.

J. SCOTT APPLEWHITE/AP



LIGHT FOUNDATIONS

Jupiter-sized planets in unexpected places spur debate.

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The birth of this chimaeric mouse suggests that the cells used to generate it behave like embryonic stem cells.

— day and night,” says Yamanaka. It will probably require more transcription factors, he adds.

If it works, researchers could produce iPS cells from patients with conditions such as Parkinson's disease or diabetes and observe the molecular changes in the cells as they develop. This ‘disease in a dish’ would offer the chance to see how different environmental factors contribute to the condition, and to test the ability of drugs to check disease progression.

But the iPS cells aren't perfect, and could not be used safely to make genetically matched cells for transplant in, for example, spinal-cord injuries. Yamanaka found that one of the factors seems to contribute to cancer in 20% of his chimaeric mice. He thinks this can be fixed, but the retroviruses used may themselves also cause mutations and cancer. “This is really dangerous. We would never transplant these into a patient,” says Jaenisch. In his view, research into embryonic stem cells made by cloning remains “absolutely essential”.

If the past year is anything to judge by, change will come quickly. “I'm not sure if it will be us, or Jaenisch, or someone else, but I expect some big success with humans in the next year,” says Yamanaka.

David Cyranoski

Additional reporting by Heidi Ledford

1. Okita, K., Ichisaka, T. & Yamanaka, S. *Nature* doi:10.1038/nature05934 (2007).
2. Wernig, M. *et al.* *Nature* doi:10.1038/nature05944 (2007).
3. Maherali, N. *et al.* *Cell Stem Cell* doi:10.1016/j.stem.2007.05.014 (2007).
4. Takahashi, K. & Yamanaka, S. *Cell* **126**, 663–676 (2006).

For more on alternative stem-cell work, see page 649; and see www.nature.com/stemcells

antibiotics, killing off the failures.

The protein Yamanaka used as a marker for stem cells last year was not terribly good at identifying reprogrammed cells. This time, all three groups used two other protein markers — Nanog and Oct4 — to great effect. All three groups were able to produce chimaeric mice using iPS cells isolated in this way; and the mice passed iPS DNA on to their offspring.

Jaenisch also used a special embryo to produce fetuses whose cells were derived entirely from iPS cells. “Only the best embryonic stem cells can do this,” he says.

“It's unbelievable, just amazing,” says Schöler, who heard Jaenisch present his results at a meeting on 31 May in Bavaria. “For me it's like Dolly [the first cloned mammal]. It's that type of accomplishment.”

The method is inviting. Whereas cloning with humans was limited by the number of available eggs and by a tricky technique that takes some six months to master, Yamanaka's method can use the most basic cells and can be accomplished with simple lab techniques.

But applying the method to human cells has yet to be successful. “We are working very hard

collaboration. Only starting the discussions on this next year sounds rather strange.”

Arriving before the annual G8 meeting of the richest nations' leaders in Germany this week, many have interpreted Bush's proposal as a tactical manoeuvre to lighten the pressure on him to agree to do anything firm about climate change at that meeting. Alden Meyer, a climate specialist at the Union of Concerned Scientists in Cambridge, Massachusetts, adds that it “could serve as a huge diversion” at the planned United Nations (UN) negotiations about climate change in Bali in December.

Others argue that Bush's proposed framework may help rather than hinder progress.

“I think that there is a good chance that whatever comes out of this process will merge into the UN process,” says Jeff Holmstead, a former environment official with the Bush administration, now at the law firm Bracewell and Giuliani in Washington DC.

Stephen Schneider, a climatologist at Stanford University in California, thinks that a side deal, separate from but not replacing the UN process, could in theory be helpful. But he says that the last such side deal initiated by Bush — the Asia-Pacific partnership of July 2005, which heavily emphasized technology developments to address climate change — is widely regarded as a flop. “It lets greenhouse gases continue to rise

at the same rate and under-funds research by a factor of 100. People who are cynical and view [the new proposal] as disingenuous have a long historical trail to base this on,” he adds.

“It remains to be seen whether this initiative means anything.”

Japan and Australia, participants in the Asia-Pacific deal, have welcomed Bush's plan. Shinzo Abe, Japan's prime minister, has said he thinks the United States is “finally getting serious in dealing with global warming”. Last week, Abe launched Japan's plan for a non-binding arrangement to halve global greenhouse-gas emissions by 2050.

China, another Asia-Pacific partner and the world's second largest emitter of carbon dioxide after the United States, also announced its plan to tackle climate change this week. It intends to focus on improving environmental management and agricultural and energy efficiencies and, like the United States, boost research and development for alternative energy, but without compromising economic development. China notes that its per-capita emissions are lower than the world average, and much lower than those of the United States. The United States, it says, should take the lead in reducing emissions. ■ Emma Marris and Colin Macilwain
Additional reporting by Quirin Schiermeier and David Cyranoski

S. OGDEN

US universities promise to go carbon neutral

In the biggest move yet to make academia carbon neutral, the leaders of more than 290 US colleges and universities have signed a pledge to reduce or offset all their greenhouse-gas emissions.

Signatories of the American College and University Presidents Climate Commitment range from large public university systems — such as the University of California — to small community colleges. All have agreed to make their plans to go carbon neutral, and their progress in achieving it, available for public scrutiny.

But it's not clear how long the universities will take to reach their goal or how much it will cost. Many are hoping that short-term savings, such as cuts in electricity bills, will help pay for longer-term changes, such as altering buildings to make them more energy efficient or buying carbon offsets to compensate for air travel.

China looks for alternative biofuel options

China is likely to stop growing food crops such as corn (maize) to make biofuels, according to a statement earlier this month by the National Development and Reform Commission.

The policy comes as demand for corn for biofuel is jumping, and prices worldwide are rising. Earlier this month, the United Nations Food and Agriculture Organization reported that worldwide import bills for coarse grains and vegetable oils — used in biofuels — are estimated to rise by up to 13% between 2006 and 2007.

In an attempt to reduce harmful emissions and decrease its need for imported oil, China plans to have 15% of its fuel coming from renewable sources, such as biofuels, by 2020. In place of corn, the China Oil and Food Corporation says it will focus on sorghum to make ethanol.



China intends to switch from growing corn to sorghum for biofuels.

More choice for space tourists

An established European space-equipment company has joined dedicated space tourism ventures such as Virgin Galactic and SpaceX in the race to take passengers to space.

Astrium, a subsidiary of the European Aeronautic Defence and Space Company, has unveiled plans for a vehicle capable of shooting four people to an altitude of 100 kilometres, giving them a 3-minute zero-gravity experience. The €1 billion (US\$1.3 billion) needed for the project is expected to come from private capital, topped up with loans and regional development funding. Astrium hopes to take its first customers up in 2012. Virgin Galactic claims it will be ready for business in 2009.

The Astrium craft will use standard jet



engines to take off and land. Once it reaches an altitude of 12 kilometres, rockets will blast the vehicle the rest of the way.

M. NEWSON/NASA

US genomics centre settles lawsuit with Icelandic firm

A new US genomics centre set up to find inherited diseases in children can continue operations, now that it has settled a potentially crippling lawsuit filed by the Icelandic firm deCODE Genetics.

Last year, deCODE sued the Center for Applied Genomics at the Children's Hospital of Philadelphia in Pennsylvania, saying that four researchers who left the firm took proprietary data with them to start the \$39-million non-profit institute. The centre plans to analyse DNA from 100,000 children.

But on 14 June, a US federal court approved a confidential settlement whereby the four researchers can conduct projects at the new centre. Both parties refused to provide details of the settlement.

Eris, not Pluto, is most massive dwarf planet

Pluto, step aside yet again. The dwarf planet known as Eris is officially the most massive dwarf planet known — heavier than the much-maligned Pluto, which the International Astronomical Union tossed out as a fully-fledged planet last year.

Michael Brown and Emily Schaller, of the California Institute of Technology in Pasadena, have now measured the mass of Eris, known informally as Xena, whose discovery was first reported in 2005. It clocks in at 16.6 billion trillion kilograms, making it 27% more massive than Pluto (M. E. Brown & E. L. Schaller *Science* 316, 1585; 2007).

These measurements were derived from new observations, made by both the Hubble Space Telescope and the Keck Observatory in Hawaii, of the orbit of Eris's moon Dysnomia. Brown and Schaller first worked out that the moon takes about 16 days to

orbit Eris. Kepler's laws of planetary motion and models detailing the gravitational pull between two objects then allowed them to calculate the planet's mass.

Boost for physical sciences in US research budget

Round one of this year's budget cycle in the United States, the first under the new Democratic-led Congress, bodes well for research.

Over the past few weeks, budget committees in the House of Representatives have given a tentative nod towards substantial increases in 2008 for several major science agencies. The Department of Energy's office of science would receive a 19% increase to US\$4.5 billion, and the National Science Foundation would see a 10% boost to \$6.5 billion.

Not all agencies will enjoy such impressive growth. The troubled research wing of the Department of Homeland Security would grow by 3% after being slashed last year to \$630 million, and the National Institutes of Health would grow by 2.6% to \$29.6 billion, which advocates of biomedical research say is not enough.

The House process is far from complete, and bills still need to be drafted in the Senate and eventually signed into law by the president. But the signs look good for research, says analyst Kei Koizumi of the American Association for the Advancement of Science in Washington DC. "It's great news," he says. "More for everyone."

Correction

In the article "Simple switch turns cells embryonic", Shinya Yamanaka is quoted as saying he has not worked with embryos before. In fact, Yamanaka used fibroblasts derived from mouse embryos for the experiments described. In other experiments outlined in the article, the same results were achieved with fibroblasts taken from postnatal skin cells.