Simple recipe gives adult cells embryonic powers

TORONTO

Reprogramming adult human cells to repair damaged tissues or organs may not be quite as tough as thought. Researchers have devised a chemical cocktail that makes adult mouse cells behave like embryonic stem cells, and the recipe is surprisingly simple.

Human embryonic stem cells can develop into all cell types in the body, an ability known as pluripotency, and scientists think these cells will be invaluable for both research and medicine. But the cells are extracted from human embryos, which is controversial in many countries. To skirt the ethical problems, scientists have been searching for alternative sources of such cells (see *Nature* 441, 1038; 2006). And little excites the field more than the possibility of a chemical recipe that can reprogramme adult cells into an embryonic state — without involving an embryo.

"Yamanaka seems to have hit a home run."

Now, Shinya Yamanaka and his colleagues at Kyoto University, Japan, have developed what looks like a good first draft for this recipe, at least in mice. They say it takes only four chemicals. For their experiment, the researchers chose fibroblasts, adult cells that divide quickly and can already give rise to some other types of cell. When they added the four factors to fibroblasts, the team says the cells looked and behaved a lot like mouse embryonic stem cells. "Potentially, if we use these four factors with human cells, we could avoid the ethical issues and make pluripotent cells," says Yamanaka.

The reprogrammed cells pass many of the crucial tests of 'stem-ness'. They express some of the key genes that embryonic stem cells do, can be coaxed to make the three main cell types of the body, and can divide to give more cells like themselves. Yamanaka calls them "embryonic-stem-cell-like cells".

Luck and skill

Yamanaka unveiled his research on 30 June at the International Society for Stem Cell Research in Toronto, Canada, revealing that success involved patience, ingenuity and luck. Over five years, his researchers compiled a list of 24 candidate factors that help stem cells stay flexible. They engineered adult mouse cells so that they would be killed by a drug unless they turned on a gene active only in stem cells. Then the team added genes for the 24 candidate factors to the engineered mouse cells, and dosed them with the drug. Only the stem-cell-like cells survived.

The researchers repeated this experiment, removing one or a few genes at a time, until they arrived at four essential chemicals. Three of the factors — Oct4, Sox2 and c-Myc — were already known to be important for stem-ness. But the fourth was a surprise, says Yamanaka. Stem-cell research is so competitive that he refuses to name this fourth factor until he can publish his work in a scientific journal.

His research adds to work on which factors are key to reprogramming. Ihor Lemischka of Princeton University, New Jersey, and his colleagues have studied 70 genes in mouse embryonic stem cells (J. Silva *et al. Nature* doi:10.1038/nature04914; 2006). And Austin Smith's team at the University of Edinburgh, UK, is investigating a protein called Nanog (N. Ivanova *et al. Nature* doi:10.1038/nature04915; 2006). "Several researchers had shown factors that were necessary for programming, but nobody had shown which factors were sufficient," says Yamanaka.

Researchers are impressed and surprised at Yamanaka's achievement, mainly because he gambled everything on the key factors being included within his pool of 24 candidates. "He seems to have hit a home run," says Lemischka.

But scientists caution that Yamanaka's report has not eliminated the need for work on embryonic stem cells. Researchers must test the same four factors in human cells. And it is not entirely clear whether the reprogrammed cells can do everything that embryonic cells can. Although many of the genes they express are the same, many are not.

Yamanaka's report came just a day after the US Senate said it would vote on relaxing rules on embryonic research later this year. Some have argued that progress in reprogramming has made work on embryonic stem cells unnecessary, and they may seize on Yamanaka's work to bolster this position. But scientists at the Toronto meeting said that would be a mistake.

"There will be people who say that, and they will be wrong," says Lemischka. "There's a lot more work to do to understand these cells. The science is really solid, but it is by no means true that reprogramming has now been solved." ■

Erika Check

ON THE RECORD

"That excommunication goes for the woman, the doctors and the scientists who eliminate the embryo."

Cardinal Alfonso López Trujillo, head of the Pontifical Council for the Family, explains how he'd like to see all those involved in embryonic stem-cell research excommunicated from the Catholic Church.

"I prayed to find a mummy, but when I saw this, I said it's better, it's really beautiful."

Nadia Lokma, chief curator of the Egyptian Museum in Cairo, says she couldn't be happier about finding embalming materials and flowers in a coffin opened in Egypt's Valley of the Kings on 28 June.

Sources: Catholic Online, Washington Post

SCORECARD

Giant beetles
Furniture makers in Wales are shocked by a huge bug in their timber. It turns out to be a rare Capricorn beetle, not seen in the country for centuries.

Stem-cell therapy
StemCells of Palo Alto announces success in treating a mouse model of Batten's disease, in which neurons lack the enzymes to break down a toxic chemical. Treatment with human fetal stem cells prolongs the lifespan of mice with this rare and fatal illness.

NUMBER CRUNCH

Good news for Britain's biomedical researchers: the finances of the Wellcome Trust are looking very healthy indeed. The trust, a medical charity that has funding clout on a par with the UK government, said on 3 July that it will raise even more money by issuing its own bonds.

£12.3 billion is the amount in the charity's endowment, up from £8.1 billion (US$14.9 billion) in 1996.

10% is the average annual return earnt by the trust's fund managers over the past ten years.

£500 million in one-off payments is the sum the charity hopes to earn by issuing bonds.

SIDELINES