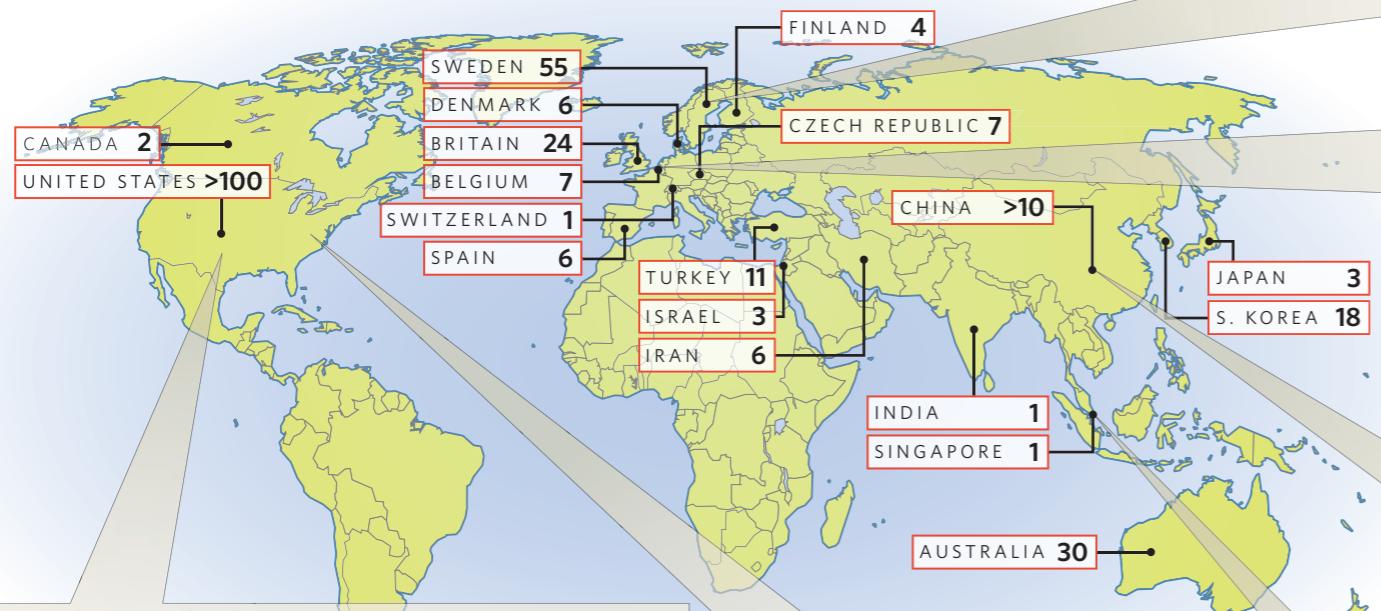


THE LURE OF STEM-CELL LINES

Nature investigates what human embryonic stem-cell lines have been derived worldwide so far, and why scientists are so desperate to work with new ones.



Drive for alternatives

In the emotionally charged stem-cell debate, to be against embryonic stem-cell research is often portrayed as being for disease. So when opponents to loosening restrictions on US funding of embryonic stem-cell research took to the Senate floor last week, they were keen to emphasize their support for research that doesn't involve the destruction of embryos (see pages 329 and 335). Some senators exaggerated the promise of adult-derived stem cells, but they have real potential, as do other alternatives to embryonic stem cells.

Adult-derived stem cells are the only form of stem-cell therapy to make it to the clinic so far. For example, stem cells from bone marrow (pictured) have been used for more than 30 years to treat blood disorders. Adult stem cells are less likely to cause

tumours than embryonic stem cells, and less likely to be rejected by the immune system.

But adult stem cells are limited in other ways — most notably supply. Some adult stem cells can be grown in the lab, but not indefinitely. Isolating sufficient quantities of certain tissues, such as brain samples, could also pose a major technical hurdle.

A few scientists are taking a different tack and trying to harvest the potential of embryonic stem cells — particularly their immortality and flexibility — without destroying embryos to get them. For example, experiments in mice have shown that a single cell taken from a blastocyst, without destroying it, can be

used to derive a cell line. But tampering with human embryos in this way may not address everyone's ethical concerns.



Diminishing returns

In August 2001, US President George W. Bush restricted federal funding to work on human embryonic stem-cell lines already in existence. Of 64 lines said to be available, some failed in culture and some were retracted by donors, leaving 21 approved lines. But why aren't scientists happy with those?

About half of the available lines grow slowly, making them virtually unusable, says Renee Reijo Pera of the University of California, San Francisco.

Another problem is that the cell lines have aged in the past five years and accumulated genetic mutations. There are frozen stocks, but many were created using protocols that

are outdated, meaning thawed cells can be difficult to culture.

Then there are the 'feeder cells' that form the matrix on which stem cells grow. All 21 lines were cultured using feeder cells from mice, so they may be too contaminated for use in humans.

There are also unexplained differences in how cell lines behave — for example, some differentiate more easily into certain cell types than others.

And researchers can't use disease-specific cell lines, which come from embryos with conditions such as cystic fibrosis: the Reproductive Genetics Institute in Chicago claims to have derived 36 such lines, but not one is approved for federally funded research.

Sweden steams ahead

At least 55 human embryonic stem-cell lines have been derived in Sweden: 30 at Cellartis in Gothenburg and 25 at the Karolinska Institute in Stockholm.

Do scientists really need so many lines to choose from? "Well, they're not all quite the same," says Outi Hovatta of the Karolinska Institute. "We've found that around 1,000 of the 30,000 genes we have checked in our cell lines are expressed differently." Each cell line

has characteristics of its own, she says.

All have the basic ability to grow in culture and to transform into different cell types. But some grow faster than others, and some are more stable in long-term culture. "Some differentiate more easily into particular tissues," adds Hovatta. "Many lines differentiate very nicely into nerve cells, for example, while others can turn into pancreatic cells, which are always rather tricky."

Europe's framework funding

A major research collaboration dedicated to human embryonic stem cells and funded by Europe's Sixth Framework Programme (FP6) kicks off next month.

The project, ESTOOLS, got €12 million (US\$15 million) from FP6, which has been matched by the collaboration, comprising 20 labs in 10 different countries. The project will study how stem cells differentiate into neurons, and will fully characterize 52 human lines. Several FP6 programmes on

specific disorders and 11 new projects have just received ethical approval for work on human embryonic stem cells (pictured). And this week EU ministers agreed to continue funding in FP7.



V. STEGER/SPL

Estimates from China

At least six laboratories in China are thought to have succeeded in deriving human embryonic stem-cell lines. Government funding for such research has significantly increased in the past five years, but there are no proper guidelines, and it is hard to monitor achievements. "There's a lot going on that you don't really know about," says

Jack Price of King's College London, who led a stem-cell team to China in 2004.

Estimates of the number of Chinese lines range from 10 to almost 70. Lingsong Li, who heads the Peking University Stem Cell Research Center, is cautious. He says that based on published evidence the most likely figure is "more than 10, but less than 15".

Clinical trials in sight

A big problem with the early human embryonic stem-cell lines is that they were not designed to be safe for use in humans. This week, Singapore-based biotech company ESI announced that it has derived four safe lines (produced in Australia) — with four more in the pipeline. It will make them available to researchers worldwide.

Regulatory agencies have not yet said what



standards cell lines would need to meet to be used in humans. But academic and biotech groups are gearing up to generate lines that satisfy Good Manufacturing Practice (GMP), a system for pharmaceutical products. Facilities that can derive and bank GMP lines are being built around the world.

It may also be possible to elevate existing lines to GMP status. The main problem with older lines is that they have been cultured with animal products. But Geron, based in Menlo Park, California, claims to have derived clinical-grade cells using two US-approved lines that were initially cultured using mouse cells. The company will apply for approval to start US clinical trials in 2007, using glial cells derived from human embryonic stem cells to treat spinal injuries.