

REGENERATIVE MEDICINE

Safety of induced stem cells gets a boost

Fears of immune response have been overestimated.

BY MONYA BAKER

A paper published in *Nature* today¹ could dispel a cloud over the hopes of turning a patient's own cells into perfectly matched replacement tissues.

Scientists first reported in 2007 that a person's cells could be reprogrammed to an embryo-like state, and so could form any type of cell in the body. Medical researchers immediately imagined using these 'induced pluripotent stem (iPS) cells' to create an endless supply of genetically matched replacement tissues to treat a range of diseases: fresh pancreatic tissue for diabetics, for example, or new nerve cells for people with Parkinson's.

The strategy also seemed to offer a way around the ethical complexities of using stem cells derived from human embryos. But then came the worries about possible side effects. Particularly bad news came from a 2011 study² showing that iPS cells provoked immune responses when injected into the mice from which they had been derived, casting doubt over one of the key advantages of the cells.

The latest *Nature* study¹ rejects that conclusion. Masumi Abe, a geneticist at the National Institute of Radiological Sciences in Chiba, Japan, and his team took iPS cells derived from mice and injected them back into the animals. For comparison, they injected other mice with embryonic stem (ES) cells. Yet unlike the 2011 study, which saw iPS cells perform worse than ES cells, the team found no differences between the immune responses of each group. The researchers also transplanted skin and bone-marrow cells derived from iPS or ES cells into mice and achieved similar success rates between the groups. The immune response of both sets of tissues is "indistinguishable", says Abe.

Konrad Hochedlinger, a stem-cell scientist at Massachusetts General Hospital in Boston, says that the result will probably "calm people down" about iPS cells. "It is definitely reassuring," he says.

The findings follow another positive study on iPS cells, published late last year³, which found that the reprogramming process causes fewer mutations than previously thought. Flora Vaccarino, a neuroscientist at Yale University in New Haven, Connecticut, and her colleagues used high-resolution DNA analysis to compare the genomes of iPS cells and the adult cells from which they were derived. They

found that most of the DNA mutations in the iPS cells did not arise during reprogramming but had been present in the parent cells.

Yang Xu, a stem-cell scientist at the University of California, San Diego, and co-author of the 2011 study², says that the new work does not dispel all concerns about the immune response provoked by iPS cells.

Xu points out that the skin and bone-marrow cells used in the latest study were not grown from iPS cells in culture, as they would be for clinical use. Instead, the researchers mixed iPS cells into early mouse embryos to make 'chimeric' embryos. They then used skin and bone-marrow tissues that arose from iPS cells after

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the embryos grew into adult mice for their transplantation experiments. It is possible, says Xu, that the most immunogenic cells were rejected as the mice developed, which would explain why Abe and his colleagues observed a limited immune response. Transplanting tissues from chimeric mice is "flawed", he says.

Producing chimeric embryos is a standard technique for testing whether mouse iPS cells have been fully reprogrammed, says Jakob Tolar, a clinician at the University of Minnesota in Minneapolis, but he notes that differentiating cells in culture outside the body is much harder. Tolar, who hopes to use iPS cells to treat the childhood skin disease epidermolysis bullosa, adds that iPS-cell therapies will use human cells, which could behave quite differently from mouse cells. "It's helpful that they've done this, but it is absolutely different when you go to something that is cultured," he says.

Hochedlinger believes that iPS cells are just as promising for cell transplantation as ES cells, although many issues stand between the lab and the clinic. The differences between the two kinds of stem cell are minor compared with the differences in how individual cell lines grow and differentiate in culture, he says.

"Based on what we know at this time from mice," he says, "iPS cells are as good as ES cells, and should be as safe." ■

1. Araki, R. *et al.* *Nature* <http://dx.doi.org/10.1038/nature11807> (2013).
2. Zhao, T., Zhang, Z.-N., Rong, Z. & Xu, Y. *Nature* **474**, 212–215 (2011).
3. Abyzov, A. *et al.* *Nature* **492**, 438–442 (2012).

should pay", says Ludovic Bernaudat, a mercury expert at the United Nations Industrial Development Organization in Vienna. "There are a lot of tensions right now."

Before the latest round of negotiations, in June 2012, the discussions aimed at an agreement for all countries to cap mercury emissions. But developing nations such as China and India — second only to China as an emitter — were adamant that this would be unfair unless developed nations helped with the cost and technologies. Common measures for controlling air pollution have the potential to reduce mercury emissions from coal plants by about 36%, "but to go further you'd need specific mercury-control technologies that can remove 90% of emissions, which are only available in developed countries", says Wang Shuxiao, an environment scientist at Tsinghua University in Beijing, who is part of the Chinese delegation.

Developed nations seem unlikely to commit to funding the transfer of such technologies. Negotiators may settle on an agreement that requires countries to set national targets that they can meet with the best mercury-control measures available to them, and to beef up monitoring programmes. UNEP predicts that such measures could reduce emissions in industrial regions by 25% by 2020, compared with an increase of up to 25% under a business-as-usual scenario.

The treaty also aims to limit emissions from artisanal gold mining, which is largely unregulated. Miners soak crushed ore in mercury to form an amalgam that leaves impurities behind; heating the amalgam frees the gold, but releases mercury into the air. "Most of them are unaware of the health hazards of mercury vapour and nobody wears a mask," says Nicola Pirrone, director of the Institute of Atmospheric Pollution Research in Rome. The treaty is likely to recommend that countries register and monitor mining, and will encourage technologies that capture mercury vapour or use jets of water and air to separate gold from ores (see *Nature* **486**, 306–307; 2012).

In late February, at the Global Ministerial Environment Forum in Nairobi, UNEP's governing council will debate the draft treaty that will emerge from next week's meeting. UNEP expects countries to ratify the treaty later this year. Even if the treaty does not set binding caps, "it should still build enough momentum for countries to commit to serious efforts to tackle the problem", says John Munthe, an environment-policy researcher at the Swedish Environmental Research Institute in Stockholm.

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"There are plenty of low-hanging fruits that could make a big difference in reducing global mercury emissions." ■