NATURE | NEWS

Lab-grown blood stem cells produced at last

Two research teams cook up recipe to make long-sought cells in mice and people.

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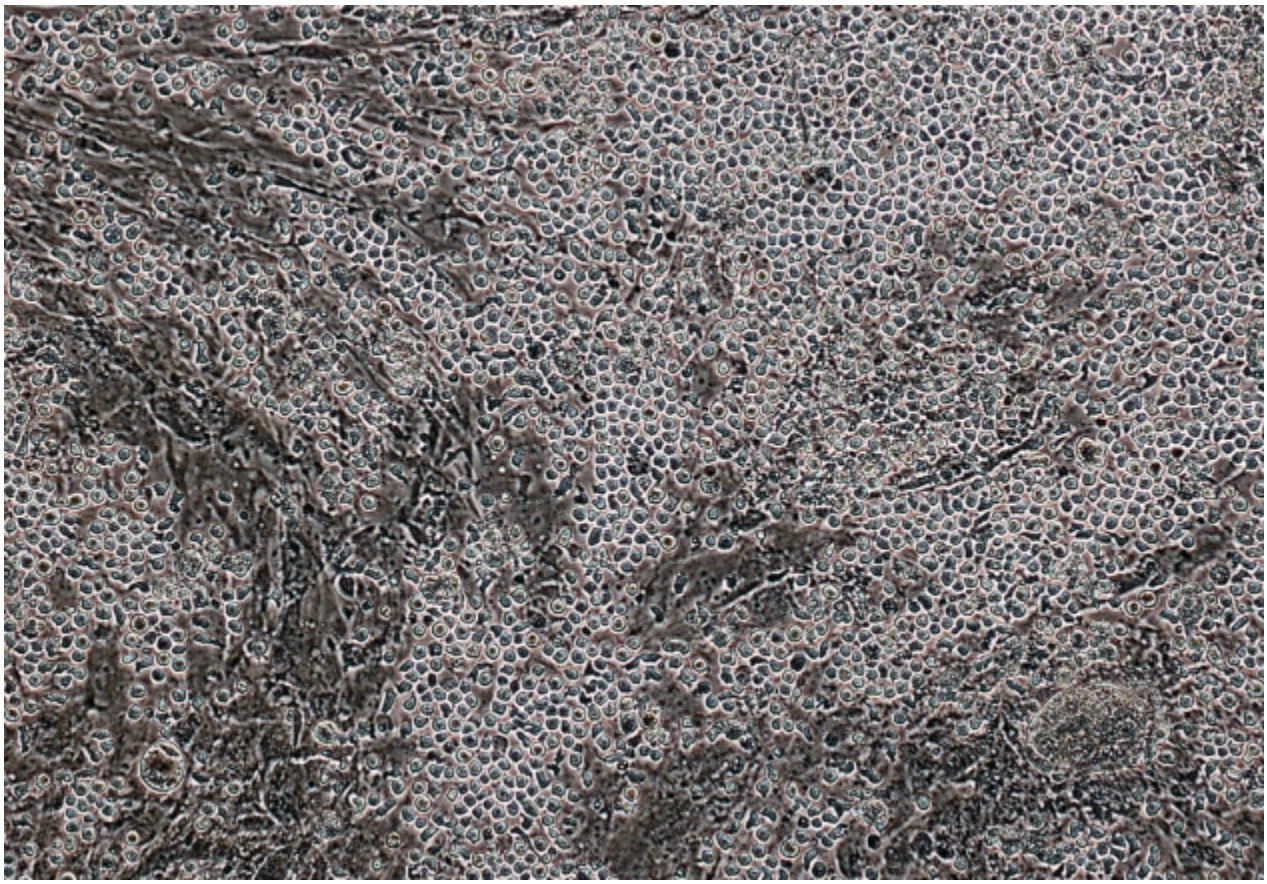

Rio Sugimura

Researchers made these blood stem cells and progenitor cells from human induced pluripotent stem cells.

After 20 years of trying, scientists have transformed mature cells into primordial blood cells that regenerate themselves and the components of blood. The work, described today in *Nature* [1, 2], offers hope to people with leukaemia and other blood disorders who need bone-marrow transplants but can't find a compatible donor. If the findings translate into the clinic, these patients could receive lab-grown versions of their own healthy cells.

One team, led by stem-cell biologist George Daley of Boston Children's Hospital in Massachusetts, created human cells that act like blood stem cells, although they are not identical to those found in nature[1]. A second team, led by stem-cell biologist Shahin Rafii of Weill Cornell Medical College in New York City, turned mature cells from mice into fully fledged blood stem cells[2].

"For many years, people have figured out parts of this recipe, but they've never quite gotten there," says Mick Bhatia, a stem-cell researcher at McMaster University in Hamilton, Canada, who was not involved with either study. "This is the first time researchers have checked all the boxes and made blood stem cells."

Daley's team chose skin cells and other cells taken from adults as their starting material. Using a standard method, they reprogrammed the cells into induced pluripotent stem (iPS) cells, which are capable of producing many other cell types. Until now, however, iPS cells have not been morphed into cells that create blood.

The next step was the novel one: Daley and his colleagues inserted seven transcription factors — genes that control other genes — into the genomes of the iPS cells. Then they injected these modified human cells into mice to develop. Twelve weeks later, the iPS cells had transformed into progenitor cells capable of making the range of cells found in human blood, including immune cells. The progenitor cells are "tantalizingly close" to naturally occurring 'haemopoetic' blood stem cells, says Daley.

Bhatia agrees. "It's pretty convincing that George has figured out how to cook up human haemopoetic stem cells," he says. "That is the holy grail."

Bloody good

By contrast, Rafii's team generated true blood stem cells from mice without the intermediate step of creating iPS cells. The researchers began by extracting cells from the lining of blood vessels in mature mice. They then inserted four transcription factors into the genomes of these cells, and kept them in Petri dishes designed to mimic the environment inside human blood vessels. There, the cells morphed into blood stem cells and multiplied.

When the researchers injected these stem cells into mice that had been treated with radiation to kill most of their blood and immune cells, the animals recovered. The stem cells regenerated the blood, including immune cells, and the mice went on to live a full life — more than 1.5 years in the lab.

Because he bypassed the iPS-cell stage, Rafii compares his approach to a direct aeroplane flight, and Daley's procedure to a flight that takes a detour to the Moon before reaching its final destination. Using the most efficient method to generate stem cells matters, he adds, because every time a gene is added to a batch of cells, a large portion of the batch fails to incorporate it and must be thrown out. There is also a risk that some cells will mutate after they are modified in the lab, and could form tumours if they are implanted into people.

But Daley and other researchers are confident that the method he used can be made more efficient, and less likely to spur tumour growth and other abnormalities in modified cells. One possibility is to temporarily alter gene expression in iPS cells, rather than permanently insert genes that encode transcription factors, says Jeanne Loring, a stem-cell researcher at the Scripps Research Institute in La Jolla, California. She notes that iPS cells can be generated from skin and other tissue that is easy to access, whereas Rafii's method begins with cells that line blood vessels, which are more difficult to gather and to keep alive in the lab.

Time will determine which approach succeeds. But the latest advances have buoyed the spirits of researchers who have been frustrated by their inability to generate blood stem cells from iPS cells. "A lot of people have become jaded, saying that these cells don't exist in nature and you can't just push them into becoming anything else," Bhatia says. "I hoped the critics were wrong, and now I know they were."

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Read the related News & Views article: 'Education for stem cells'

References

1. Sugimura, R. *et al*. *Nature* http://dx.doi.org/10.1038/nature22370 (2017).
2. Lis, R. *et al*. *Nature* http://dx.doi.org/10.1038/nature22326 (2017).