Fresh questions on stem cell findings

The discovery of more duplicated data is again casting a shadow over "versatile" adult stem cells

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FRESH questions surround some of the highest-profile research on adult stem cells. For the second time, *New Scientist* has discovered apparently duplicated data being used to describe results from different experiments in work published by a group of scientists at the University of Minnesota, Minneapolis.

The research relates to a particular type of adult stem cell that appears to have a remarkable ability to turn into many types of tissue. This type of cell has been promoted by some activists and politicians as an alternative to human embryonic stem cells in medical research. The use of ESCs is unacceptable to some people because they can only be harvested from embryos that are destroyed in the process.

In June 2002, Catherine Verfaillie's team at Minnesota published a paper in *Nature* (vol 418, p 41) describing a population of stem cells from the bone marrow of mice that seemed able to grow into most of the body's tissues. This was a surprise, because adult stem cells can generally form only a narrow range of tissue types. Verfaillie's team called these cells "multipotent adult progenitor cells" or MAPCs. Other researchers have since found it difficult to replicate the work (see "A hard act to follow").

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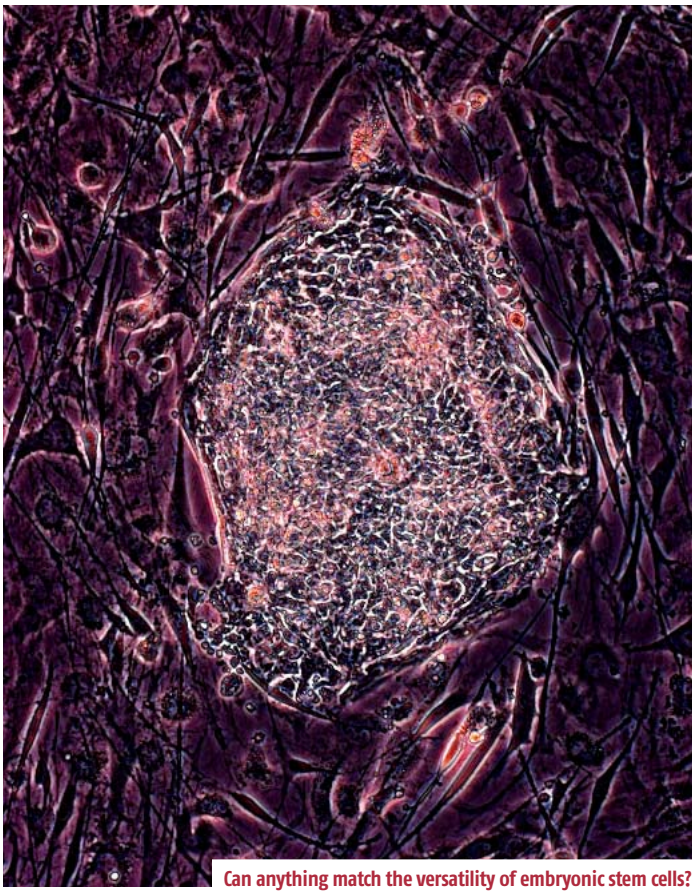
Given these difficulties, *New Scientist* decided more than a year ago to take a close look at the *Nature* paper. We found that some of the images within it also appeared in a second paper that was published at about the same time, where they were supposed to relate to a different experiment (see "Flaws and duplications").

Now *New Scientist* has examined a US patent (number 7015037) granted in 2006 that covers the isolation and use of MAPCs. The patent is exclusively licensed to a company called Athersys of Cleveland, Ohio, which hopes to launch clinical trials of the cells to treat conditions including heart attacks and stroke.

Within the patent are three images that appear to be duplicated from another paper from Verfaillie's group, published in 2001 in the journal *Blood* (vol 98, pp 2615-2625). These images relate to experiments in which MAPCs were grown in culture dishes and made to differentiate into other cell types, such as those found in bone, cartilage, fat and the linings of blood vessels. The images document the presence of proteins specific to each type of cell being produced.

The problem is that in each case the duplicated image is used in the patent to describe the production of a different protein from that described in the *Blood* paper.

In the most striking example, one of the duplicated images also seems to be used twice within the *Blood* paper itself, to represent the results from two different experiments. In the *Blood* paper, this image, which shows a series of three bands on a gel, is first



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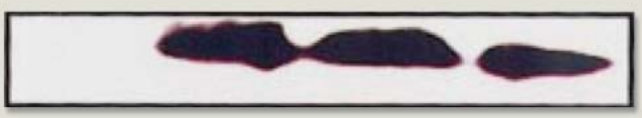
Can anything match the versatility of embryonic stem cells?

SPOT THE DIFFERENCE

These apparently duplicated images have been used as evidence for the presence of different proteins produced in different experiments

- First, an image of three bands on a gel is used to represent a control for an experiment in which stem cells are made to differentiate into bone cells (*Blood*, vol 98, p 2620)

- On the same page of the *Blood* paper, a reversed version of the same image, with some small modifications, is used to show the production of collagen II in stem cells made to differentiate into cartilage cells



- The same reversed image is used in US patent 7015037 to show the production of a bone-specific protein in stem cells made to differentiate into bone cells

SOURCE: BLOOD (VOL 98, P 2620) AND US PATENT 7015037

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used to represent a control for an experiment in which a culture of stem cells is made to differentiate into cells found in bone. What seems to be the same image is used later on the same page, though this time it is flipped over horizontally, producing a mirror image, and contains some small modifications (see top two images, below left). Here, it is labelled as showing the production of collagen in a culture of stem cells made to turn into cells found in cartilage.

In the patent, this flipped and modified image appears again, this time supposedly representing a bone-specific protein found in a culture of stem cells made to differentiate into bone cells (see bottom image, below left).

The research described in the *Blood* paper formed part of the PhD work of its first author, Morayma Reyes, and the duplicated images in the paper, including the flipped and modified version, also appear in her thesis. Now at the University of Washington in Seattle, Reyes is named on the patent as one of the inventors, along with Verfaillie, who was her supervisor, and Leo Furcht, who heads the department of laboratory medicine and pathology at the University of Minnesota. Currently president of the Federation of American Societies for Experimental Biology, Furcht founded a company called MCL that was assigned the patent jointly with the University of Minnesota.

Stem cell biologists contacted by *New Scientist* are sure that the three images referred to above are duplicates. "They're quite clearly the same," says Jeanne Loring of the Burnham Institute for Medical Research in La Jolla, California. "It appears that a piece of data has been used multiple times to represent different things," agrees Arnold Kriegstein, who heads the programme in developmental and stem cell biology at the University of California, San Francisco.

"The *Blood* paper is significant because it describes cells isolated from the bone marrow of human volunteers"

Although the *Blood* paper is less well known than the publication that followed in *Nature*, it is significant in terms of the planned clinical trials because it describes cells isolated from the bone marrow of human volunteers rather than experimental mice.

Verfaillie, who is now at the Catholic University of Leuven (KUL) in Belgium, and Reyes were unavailable to respond to questions from *New Scientist* asking for an explanation of the apparent duplications. Athersys said it would review the points we raised, while the University of Minnesota said it had no comment.

After being contacted by *New Scientist*, *Blood* is now conducting its own inquiry. "We're going to do a serious investigation into this," says the journal's editor-in-chief, Sanford Shattil, a haematologist at the University of California, San Diego. ●

A HARD ACT TO FOLLOW

Everyone can agree on one thing about Catherine Verfaillie's stem cells, known as MAPCs: they are fiendishly difficult to work with. Isolating MAPCs requires careful laboratory culture, following a complex recipe, and some researchers who have tried to follow this recipe have never been able to obtain MAPCs.

The flaws that Verfaillie has acknowledged with experiments describing "marker" molecules carried on the cells' surfaces may have contributed to these difficulties. But in a letter to *Nature* sent last month Verfaillie suggested otherwise, saying that later papers by her research group confirm the marker profiles originally published in *Nature*.

Nevertheless, Verfaillie and her colleagues have changed details of their culture methods over time, after being unable to isolate MAPCs themselves for more than six months from late 2003. The description of the cells in her most recent papers is also different in some respects: for instance, they are now said to carry a marker called c-kit, which they did not in the *Nature* paper.

"It remains unclear whether the later studies have used a different population of cells, or the same cells that look somewhat different under different culture conditions," says Sean Morrison, a stem cell biologist at the University of Michigan, Ann Arbor.

While Verfaillie says several groups have repeated aspects of her work, no one has reproduced the most exciting experiment in the *Nature* paper. This showed a section through a mouse that had been injected early in its embryonic development with a single MAPC, and was stained to show that the cell had contributed to most of the animal's tissues. Previously, only embryonic stem cells had passed this test.

Rudolf Jaenisch at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, says that a member of Verfaillie's team, Yuehua Jiang, visited his lab with a culture of MAPCs before the *Nature* paper appeared, to try and repeat the experiment. He did not succeed, Jaenisch says, and after Jiang had gone the Whitehead team was unable to get the cells to grow.

Jiang could not be reached for comment. Jaenisch says that because MAPCs divide much more slowly than the cells found in mouse embryos, he always doubted they could compete with embryonic cells and produce the striking result reported in *Nature*.

FLAWS AND DUPLICATIONS

When *New Scientist* started to investigate Catherine Verfaillie's work on the stem cells known as MAPCs, in December 2005, we soon found that six plots from her *Nature* paper and its online supplementary information, published in June 2002, also appeared in a paper published in August that year in *Experimental Hematology* (vol 30, p 896) – where they were supposed to relate to different cells, taken from different mice.

The plots in question describe distinctive "marker" molecules carried on the surface of the cells. When we approached Verfaillie in February 2006, she told us that the figures were compiled by a researcher in her lab, Yuehua Jiang, and referred the matter to the authorities at the University of Minnesota. That same month, she sent a correction to *Experimental Hematology*, acknowledging some plots were from the *Nature* paper.

In August 2006, the university convened an inquiry panel of three scientists to examine the duplications, which the following month accepted that they were the result of an honest error. But the panel raised a second problem. Two of its members were specialists in the technique used to examine the markers, and they said there were "serious concerns about the quality" of these results. Specifically, there were problems with the control experiments used for comparison to judge whether or not a particular marker was present.

Neither of these scientists was a stem cell biologist, so specialists in this field were then asked to conduct an independent scientific review. After two stem cell experts provided their comments, Verfaillie wrote last month to *Experimental Hematology* and to *Nature*, informing them that plots in the papers "should not be relied upon as accurate representations of MAPC marker profiles" (*New Scientist*, 17 February, p 12). *Experimental Hematology* is publishing her letter; *Nature* is seeking expert advice before deciding how to proceed.