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Shoukhrat Mitalipov, lead author of human stem-cell cloning paper, admits errors.

STEM CELLS

Fallout from hailed cloning paper

Duplicated figures raise debate over expedited publication.

BY DAVID CYRANOSKI

How fast is too fast for review of a scientific article? And who has the responsibility to ensure accuracy? Errors found in a widely acclaimed cloning study have rekindled those questions — and sent the lead author and the journal that published it scrambling to assure the world that the problems did not compromise the findings.

The paper, which was published online by the journal *Cell* on 15 May (<http://doi.org/mkn>), reported the creation of human embryonic stem-cell lines from cloned human skin cells. The lines are expected to answer fundamental questions about the way in which cells are reprogrammed and also to have potential

therapeutic applications.

But last Wednesday, after an anonymous online commenter noted three pairs of duplicated images with conflicting labels in the paper, excitement turned to confusion — and a bit of déjà vu. The last time the same feat was claimed — by then Seoul University professor Woo Suk Hwang — duplicate images were noted anonymously and the breakthrough was later debunked. Nobody is claiming more than sloppiness in the present case, and the authors quickly stepped up to put the record straight.

The leader of the study, Shoukhrat Mitalipov, a reproductive-biology specialist at the

Oregon Health and Science University in Portland, acknowledges that the team did use three sets of duplicated images. In two cases that was intentional, but a pair of labels was mistakenly reversed, he says (see <http://doi.org/mnk>).

In the third case, an incorrect scatterplot was included in a table examining the patterns of gene activity in the cloned stem-cell lines — one that had already been used in the paper.

Mitalipov says that corrections will be made. He waves off another criticism raised by the anonymous commenter concerning the surprisingly tight shape of two scatterplots: they just turned out that way, he says.

“The results are real, the cell lines are real, everything is real,” he says.

The editor-in-chief of *Cell*, Emilie Marcus, released a statement in response to the criticisms, defending the paper: “Based on our own initial in-house assessment of issues raised and in initial discussions with the authors, it seems that there were some minor errors made by the authors when preparing the figures for initial submission. While we are continuing discussions with the authors, we do not believe these errors impact the scientific findings of the paper in any way.”

Most researchers seem ready to give Mitalipov the benefit of the doubt, on the basis of his answers and his track record. “The explanations [by Mitalipov] are plausible, but we will have to wait for the results of a thorough investigation,” says Martin Pera, a stem-cell expert at the University of Melbourne, Australia.

Robin Lovell-Badge, a developmental biologist at the Medical Research Council’s National Institute for Medical Research in London, also accepts that the errors resulted just from sloppiness. “I really don’t think in this case it’s any attempt to manipulate. It’s not the data you would want to manipulate, anyway,” he says.

But many also noted that the paper had been published with blazing speed — *Cell* accepted it just three days after receiving it and published it online 12 days later — and questioned whether such rapid publication is good for science. “Whatever the explanation is, it’s amazing that there is another issue with a paper in SCNT [somatic-cell nuclear transfer]. The four-day review process was obviously inadequate,” says Arnold Kriegstein, director of the stem-cell programme at the University of California, San Francisco. ▶

NATURE.COM
For more on the cloning breakthrough go to:
go.nature.com/tejh2

► Lovell-Badge says that the mistakes still should have been caught, by both the authors and the reviewers and the journal, particularly one staffed by a team of professional editors. “It’s the author’s problem but if it’s a journal like *Cell* or *Nature*, then I think, the journal, they have to take some responsibility to make sure there are no errors,” he says.

Veronique Kiermer, executive editor at Nature Publishing Group, says that “this type of image manipulation is not something we expect referees to pick up. It’s not really their role.” She says that the *Nature* journals do “spot-checking” — on average, of two papers per issue. “But duplications between different figures, or between supplementary figures and the main text, are difficult to pick up,” she says.

Mike Rossner, former executive director of the Rockefeller University Press, implemented image screening as part of the press’s review process in its journals, such as the *Journal of Cell Biology*, in 2002. He says that all journals should do the same. Rossner says that inappropriately manipulated images appeared in as many as 25% of articles checked, although only about 1% affected the interpretation of the data. “I cannot speculate on whether our image-screening process would have caught these particular issues [in Mitalipov’s *Cell* paper], but the process does include a visual check for duplicated regions in a figure,” he says.

Marcus defends the fast peer review: “It is a misrepresentation to equate slow peer review with thoroughness or rigor or to use timely peer review as a justification for sloppiness in manuscript preparation,” she wrote in her statement.

Mitalipov admits that a rush to publish might have led to mistakes that he compares to “typos.” But if he had to do it over, he says he wouldn’t take any more time or do anything differently — other than to “make sure the errors weren’t there.”

“We had four cell lines in December. We had five months to put together data. Most images and most figures were ready months in advance. The project was done, completed, written,” he says.

“If you have a paper that’s that hot, it will go through quickly. Other projects will take more time,” he says. “It’s better than [it] sitting on someone’s desk for 6 months.”

Mitalipov is arranging to give about a dozen other groups access to the cells, which would allow them to validate the cell lines. “The first thing we want to do is have people confirm our results,” he said. “We are not hiding these cell lines.” ■

Additional reporting by Ewen Callaway, Erika Check Hayden and Richard Van Noorden.

CANCER

Immunotherapy’s cancer remit widens

Combination therapies hold great promise, but at what cost?

BY HEIDI LEDFORD

Drugs that unleash the power of the immune system on cancers are generating considerable optimism in industry, but still Andrew Baum thinks analysts are selling them short. In a 22 May report, Baum, the London-based head of global health-care research at the investment bank Citi, forecasts that in ten years the drugs will be treating 60% of cancers and earning US\$35 billion a year.

Three elements contribute to his bullishness: the drugs are showing signs of wider effectiveness; many patients will take them for years; and the prices are stratospheric (see ‘Stiff medicine’).

One of the first such drugs to be approved, Yervoy (ipilimumab), costs about \$40,000 per month in the United States, and £15,000 (\$23,000) in the United Kingdom, where health-care officials negotiated a lower price. So far, expensive immunotherapies have been approved only for treating melanoma and prostate cancer. But this weekend, at the annual meeting of the American Society of Clinical Oncology in Chicago, Illinois, investigators will present promising results from trials that indicate that immunotherapies could soon have a role in treating cancers of the lung, kidney and stomach.

A new strategy will add to the costs: regimens that combine the drugs with radiation therapy, genetically targeted drugs and other immunotherapies. The hope is that these other treatments will enhance the ability of the immune system to recognize the tumour, either by further stimulating the immune system, or by

damaging the tumour so as to release antigens that the immune system recognizes.

Yervoy, made by Bristol-Myers Squibb, headquartered in New York, is remarkable because a three-month course can send cancer into remission for years (see go.nature.com/k1e3m2). However, only about one-quarter of patients with advanced melanoma responds to the drug, which spurs tumour-killing T cells into action by blocking an inhibitory signal. “When Yervoy was first approved in 2011, we all recognized that it was an important moment for the field,” says Jedd Wolchok, an oncologist at the Memorial Sloan-Kettering Cancer Center in New York. “But it was also a call to do better.”

On 2 June, Wolchok will present data from a trial that combined Yervoy with an experimental drug called nivolumab, also made by Bristol-Myers Squibb. It releases a second brake on the immune system by stifling a different protein. The number of patients in the trial was small, but the results suggest that melanomas shrank in half of those who received the highest two doses tested.

Combination approaches could expand the number of cancers that respond to immunotherapy. But they could also accelerate the rise in the cost of cancer care. US spending on cancer drugs is rising by some 15% a year, twice as fast as health-care costs overall. “Cancer is a very complicated and expensive disease,” says Scott Ramsey, a health-care economist at the Fred Hutchinson Cancer Research Center in Seattle, Washington. “But now it’s turning into a chronic disease, and we’re talking about years of maintenance therapy with drugs that cost \$10,000 a month.” However, not all of the inflation is due to expensive new drugs, says Ira Klein, a medical director at insurance company Aetna, based in Hartford, Connecticut. The price of radiation therapy is rising by 25% per year, he notes, driven by new technologies that can cost \$100,000 or more for a full course of treatment.

Drug developers attribute the high cost of the drugs to the expense of research and development, which is compounded by the industry’s high failure rate. Wolchok notes that drugs such as Yervoy have a small market, and speculates that prices may fall once their markets expand to other cancers. But Peter Bach, who studies health-care policy at Memorial Sloan-Kettering, is sceptical that industry will cut prices. “I have never seen that,” he says. “I have only seen the opposite.” ■

STIFF MEDICINE

The cost of treating cancer is surging, with immunotherapies at the fore.

PETER BACH