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Born or made? Debate on mouse eggs reignites

Experiments published this week fuel the controversy about whether mammals are born with a fixed pool of egg cells or can make fresh eggs. The issue is divisive not just because it challenges 50 years of scientific dogma. If women could generate new eggs it would have huge implications for fertility treatments, menopause, and even cell-based therapies.

Last year, a controversial paper[1] by Jonathan Tilly and his colleagues at Harvard Medical School proposed that egg cells can arise from bone marrow and other circulating cells[2]. But Amy Wagers, also at Harvard Medical School, and her colleagues now report that this is not the case, at least for ovulated eggs[3]. Some critics think the new study proves Tilly's work was flawed, but Tilly and other experts say that some aspects of egg renewal remain open questions.

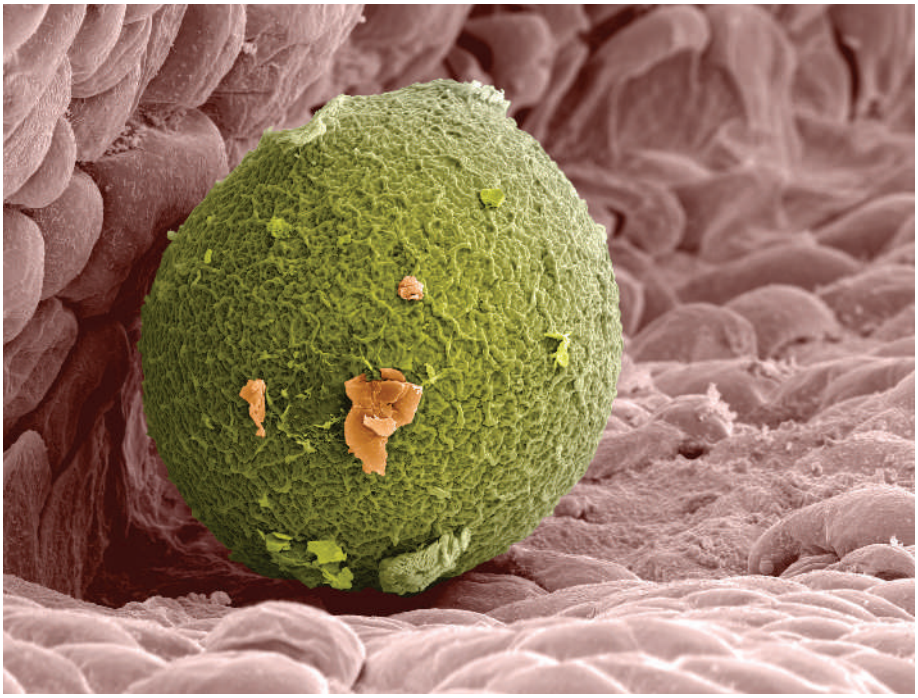
Tilly's bone-marrow study drew loud criticism from others in the field, both in the press and the literature. But without experimental testing of the ideas, much of the disapproval rang hollow. Now, Wagers and her colleagues have addressed the bone-marrow hypothesis. "This is a pretty powerful denial of the idea that new eggs form and contribute to fertility," says co-author Roger Gosden of Cornell University's Weill Medical College in New York.

Tilly's study found that a bone-marrow transplant from a donor mouse expressing a green fluorescent marker called GFP in all its cells resulted in green eggs — presumably newly generated — in the ovary of a normal mouse recipient.

To test that idea, Gosden and Wagers linked the circulatory systems of paired mice — one normal, and one with GFP. After several months, the researchers induced ovulation in both animals. Normal mice ovulated only normal eggs; GFP mice ovulated only green eggs, showing that there had been no exchange of egg-generating stem cells.

"It incontestably shows that the Tilly work was simply not true," says ovarian researcher David Albertini of the University of Kansas Medical Center in Kansas City. Echoing that sentiment, reproductive biologist Evelyn Telfer at University of Edinburgh, UK, is also unconvinced by Tilly's data, adding that the story changes as new data come in.

"Science is supposed to be a moving target," retorts Tilly. "Whether our data are repeatable is valid, but no one as yet has disproved any of our data." Tilly has several technical issues with the Wagers study, but he is most disturbed by the comparison of his work, which examined the pool of immature egg cells inside the ovary, to this study, which examines ovulated eggs outside the ovary.



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Seed of doubt: biologists are divided over whether adult mammals can regenerate egg cells.

He argues that circulating stem cells may still become immature egg cells inside the ovary. Such immature cells, he points out, are critical to fertility and hormonal balance, even if they are never ovulated. And he stands by the bone-marrow connection, pointing to additional experimental data from his group currently under review.

"This is a pretty powerful denial of the idea that new eggs form and contribute to fertility."

Embryonic idea

Albertini says this explanation is "looking to keep something of the original idea alive". He and other critics question why regeneration would occur in the immature but not the ovulated population of cells: "It's a bit of a stretch."

But several other experts agree that because Wagers's study did not examine immature cells inside the ovary, it leaves room for possible regeneration and the hunt for the responsible stem cells. But even if that were the case, all admit that it is a huge leap to suggest that the same happens in humans.

For now, regeneration in mice "is still an open issue", says Jeff Kerr of Monash University in Clayton, Australia. At least, "until someone comes up with some killer experiments to prove that bone marrow, or the ovary, is, or is not, the source of new oocytes". Kerr, Jock Findlay and colleagues add a piece of support for regeneration in research to be published online later this month[4].

They found that the mouse strain used by Tilly and Wagers maintains a steady pool of oocyte numbers from before puberty into middle age, rather than the number declining with age as the dogma holds. Whether that is due to regeneration is unknown, says Kerr, but such a possibility would not be "completely out of left field".

Even Gosden, one of Tilly's more vocal critics, leaves the door open to the possibility of regenerative, albeit dormant, egg stem cells. "Our work suggests they do not contribute to new ovulations, but perhaps under special circumstances they could be brought back to life [in the lab dish]," he says. "I think the Tilly group might be right to some extent on that one." ■

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1. Johnson, J. *et al. Cell* **122,** 303–315 (2005).
2. Ainsworth, C. *Nature* **436,** 609 (2005).
3. Eggan, K. *et al. Nature* doi:10.1038/nature04929 (2006).
4. Kerr, J. *et al. Reproduction* doi:10.1530/rep.1.01128 (2006).