Two dads, one baby? Gene technique works in mice

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For the first time in history, scientists have created mice with two dads, foretelling a day when same-sex couples may be able to have biological children of their own.

The success, announced by Japanese researchers last month, has not yet been tried on people.

But scientists at two Bay Area startups, as well as a company in New York City and another in Japan, are striving to move the mouse research into humans, and rewrite the rules of reproduction by making sex cells in a lab. If successful in people, the technique would allow the creation of an egg cell from blood or a tiny sliver of a man or woman's skin.

So far, the research has focused on making egg cells, which would enable male-male reproduction. Creating sperm for female-female reproduction is a tougher scientific challenge.

"Even the remote possibility of same-sex couples creating a baby without a donor is extraordinary and exciting," said Drew Lloyd, board president of the Bay Area Municipal Elections Committee, which advocates for the civil rights of LGBTQ people. "I've learned not to put limits on what's possible."

Both Bay Area companies are secretive about the progress of their research and would not consent to interviews. The Berkeley-based startup Conception, with 34 employees and at least $20 million in private funding, seeks to create human eggs using stem cells from human blood samples. The other company, San Francisco's Ivy Natal, aims to build eggs with a skin biopsy.

The new research, described by Katsuhiko Hayashi of Osaka University in the March 15 issue of the journal *Nature*, marks a milestone in reproductive biology.

The Japanese team guided stem cells from a male mouse to form eggs, which were fertilized by another male mouse. The two mice conceived seven pups who were healthy and fertile, eventually conceiving babies of

their own.

But the project's success rate was extremely low. About 30% of the male mouse's stem cells matured into eggs, and 40% of those eggs were successfully fertilized to create embryos. The embryos were transferred to a surrogate female mouse to gestate, but only 1%—7 out of 630—were born alive.

Experts said it is not yet known whether the strategy would work in humans.

"Mice aren't people," said Hank Greely, director of the Center for Law and the Biosciences at Stanford University. "And it's a complicated method."

UC San Francisco developmental biologists Jonathan Bayer and Diana Laird agreed, writing "we have much to learn before we use cultured stem cells to make human eggs in a dish," in an article that accompanied the Nature paper.

The technique, called in vitro gametogenesis or IVG, builds on the Nobel Prize-winning work of Dr. Shinya Yamanaka, a biologist at Japan's Kyoto University who is also affiliated with San Francisco's Gladstone Institute. In 2007, Yamanaka described how to create stem cells by reprogramming skin cells, turning them into "induced pluripotent stem cells," or iPSCs. These iPSCs can be coaxed into becoming nearly any cell type in the human body, from brain to liver—and perhaps, someday, human egg or sperm.

The latest work was technically complex and required many steps. First, the team took skin cells from the tail of an adult male mouse. Then it reprogrammed these skin cells to become stem cells.

The biggest challenge was converting these stem cells from male to female. Because the production of mature eggs requires two copies of the X chromosome, the authors devised a way to find rare male stem cells that jettison their Y chromosome and then duplicate their X chromosome.

Once chromosomally female, these cells were biochemically nudged to turn into immature eggs.

The team tried, but failed, to make sperm from female cells. So two female mice could not conceive together. That's because there's not yet a successful technique for converting a cell with two X chromosomes into a Y chromosome—and without a Y chromosome, no sperm can be made.

In 2017, researchers in China created healthy mice with two mothers, but it involved a tremendous amount of gene editing with CRISPR, making it impractical to use for anything other than research. They also made mice with two dads, but the offspring quickly died.

But the breakthrough opens up exciting new avenues in reproductive biology and fertility research.

For instance, it could be used to rapidly produce inbred strains of identical mice, useful for laboratory experiments. It also offers a strategy to propagate endangered mammals from a single male.

It could also make replacement eggs for older women to have children, as well as couples who are infertile due to congenital problems, an accident, disease or treatment such as chemotherapy.

And it would offer same-sex or transgender couples the chance to have their own biological children. Currently such couples must use the eggs

or sperm from one person, and the eggs or sperm from a donor.

Adoptive parent Johnny Symons, professor in the School of Cinema at San Francisco State University whose documentary film Daddy & Papa focuses on the experience of gay men raising children through adoption and surrogacy, called family-building "an incredibly personal decision."

"Having biological families has been least accessible to us," he said. "This technology stands to be a real breakthrough in terms of providing options for people who want that."

"If the technology advances, it could really change societal perceptions of gay men as parents, and potentially legitimize us in a new way," said Symons. "There's something very powerful and undeniable about physical resemblance. … It makes it harder for people who oppose us to deny us political rights or equal social standards."

But there's a darker side to making sex cells in the lab, said Greely, author of the 2016 book, "The End of Sex and the Future of Human Reproduction."

"If this worked," he said, "you could make eggs from sperm from 8-year-olds. You could make eggs from sperm from fetal remains. You could make eggs from sperm from somebody who has been dead for years, but whose cells were frozen. That gets a little weird."

Someday, perhaps, it may be possible to create both eggs and sperm from the same person, creating what Greely calls a "unibaby." "You're pregnant—by yourself," he said. "I can't imagine a good reason to do this."

Even if the technique works in humans, it must first be proven safe, experts agree. Created through genetic manipulation, embryos may have

hidden defects. There must be wider societal debate and regulatory oversight.

The next step is to test the technique in monkeys or chimpanzees.

Fertility experts, such as the American Society for Reproductive Medicine's Research Institute, think it's on the horizon.

"If we can do this properly and safely and we can bring the cost down to being something accessible for everyone," said Conception CEO Matt Krisiloff in a company video, "I really think there's a possibility that this could become the default way people choose to have children."