BLACKOUT CONCEPTS / ALAMY

Happy families

'3-parent baby' success

A healthy boy is the first to be born using a new technique that uses DNA from three people, reports **Jessica Hamzelou**

IT'S a boy! A 5-month-old baby is the first to be born using a new technique that incorporates DNA from three people. "This is great news and a huge deal," says Dusko Ilic at King's College London, who wasn't involved in the work. "It's revolutionary."

The controversial technique, which allows parents with rare genetic mutations to have healthy babies, has only been legally approved in the UK. But the birth of the baby, whose Jordanian parents were treated by a US-based team in Mexico, should fast-forward progress around the world, say embryologists.

The mother carries genes for Leigh syndrome, a fatal disorder that affects the developing nervous system. Genes for the disease sit in DNA in the mitochondria, which provide energy for our cells and carry just 37 genes that are passed down to us from our mothers. This is separate from the majority of our DNA, which is housed in each cell's nucleus.

Around a quarter of the mother's mitochondria have the disease-causing mutation. While she is healthy, Leigh syndrome was responsible for the deaths of her first two children. She and her husband sought out the help of John Zhang (pictured below) and his team at the New Hope Fertility Center in New York City.

Zhang has been working on a way to avoid mitochondrial disease using a so-called "three-parent" technique. In theory, there are a few ways of doing this. The method approved in the UK is called pronuclear transfer and involves fertilising both the mother's egg and a donor egg with the father's sperm. Before the fertilised eggs start dividing into early-stage embryos, each nucleus is removed. The nucleus from the donor's fertilised egg is discarded and replaced by that from the mother's fertilised egg.

"The mother carries genes for Leigh syndrome, but the child shows no signs of the disease"

But this technique wasn't appropriate for the couple – as Muslims, they were opposed to the destruction of two embryos. So Zhang took a different approach, called spindle nuclear transfer. He removed the nucleus from one of the mother's eggs and inserted it into a donor egg that had had its own nucleus removed. The resulting egg – with nuclear DNA from the mother and mitochondrial DNA from a donor – was then fertilised with the father's sperm.

Zhang's team used this approach to create five embryos. They chose the male embryo that was of the highest quality to implant in the mother. Their baby was born nine months later. "It's

TWO WOMEN, ONE MAN AND A BABY

A Jordanian couple have been trying to start a family for almost 20 years. Ten years after they married, she became pregnant, but it ended in the first of four miscarriages.

In 2005, the couple gave birth to a baby girl. It was then that they discovered the probable cause of their fertility problems: a genetic mutation in the mother's mitochondria. Their daughter was born with Leigh syndrome, which affects the brain, muscles and nerves of developing infants. Sadly, she died aged 6. The couple's second child had the same disorder, and lived for 8 months.

Using a controversial "three-parent baby" technique (see main story), their third child was born on 6 April 2016. He is showing no signs of disease.

exciting news," says Bert Smeets at Maastricht University in the Netherlands. The team will describe the findings at the American Society for Reproductive Medicine's Scientific Congress in Salt Lake City in October.

Neither method has been approved in the US, so Zhang went to Mexico instead, where he says "there are no rules". He is adamant that he made the right choice. "To save lives is the ethical thing to do," he says.

The team seems to have taken an ethical approach with their technique, says Sian Harding, who reviewed the ethics of the UK procedure. They avoided destroying embryos, and used a male embryo, so that the resulting child wouldn't pass on any inherited mitochondrial DNA, she says. "It's as good as or better than what we'll do in the UK."

A remaining concern is safety. Last time embryologists tried to create a baby using DNA from three people was in the 1990s, when they injected mitochondrial DNA from a donor into another woman's egg, along with sperm from her partner. Some of the babies went on to develop genetic disorders, and the company performing the technique were advised to halt it. The problem may have arisen from the babies having mitochondria from two sources.

When Zhang and his colleagues tested the baby's mitochondria, they found that less than 1 per cent carry the mutation. Hopefully, this is too low to cause any problems; generally it is thought to take about 18 per cent of mitochondria to be affected before problems start. "It's very good," says Ilic.

Smeets agrees, but cautions that the team should monitor the baby to make sure the levels stay low. There's a chance that faulty mitochondria could be better at replicating, and gradually increase in number, he says. "We need to wait for more births, and to carefully judge them," says Smeets. ■

Deadly amoeba hunts down brain chemical

ALL it takes is a splash. Brain-eating amoebas (pictured below, in orange) can enter an unwary swimmer's brain via their nose, and once that happens, their chances of survival are slim. "They have these food cups on their surface, which are like giant suckers," says Francine Cabral of Virginia Commonwealth University in Richmond. "They'll just start eating the brain."

Now, researchers have discovered why this deadly amoeba has such an affinity for the brain – a breakthrough that could lead to life-saving drug treatments.

The amoeba, *Naegleria fowleri*, tends to lurk in fresh water, although infections can also result from swimming in hot springs or improperly chlorinated pools. Of the 35 reported cases in the US between 2005 and 2014, only two people survived. Last month, a 19-year-old woman died after being infected in Maryland.

After the amoeba enters the body, it ignores the nose and heads straight to the brain, where the first areas it destroys are the olfactory regions that we use to smell, and parts of the frontal lobe, which are crucial for cognition and controlling our behaviour.

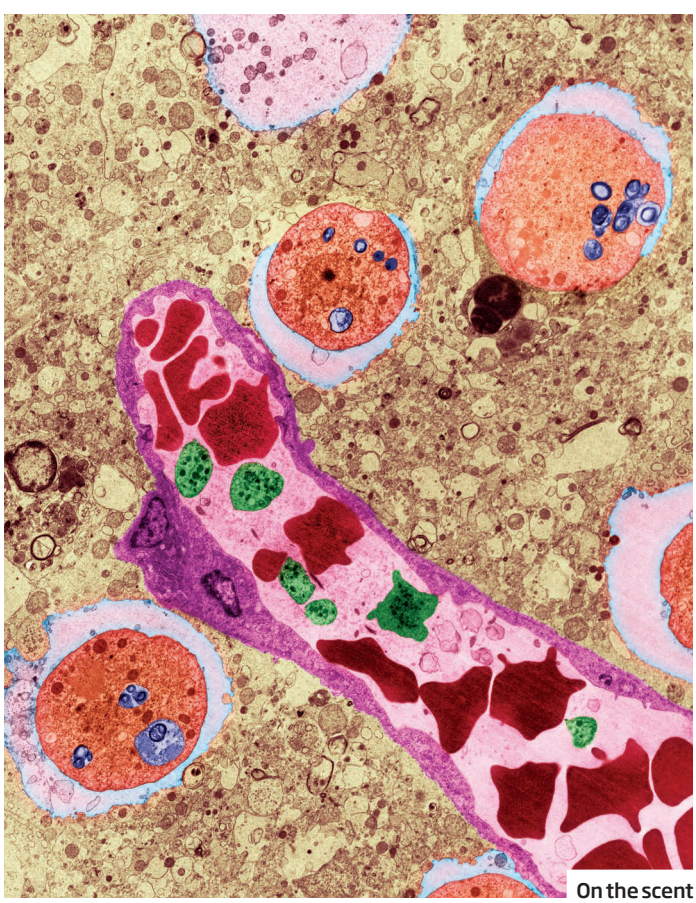
Why they specifically target the brain is a mystery. Abdul Mannan at the Aga Khan University in Karachi, Pakistan, suspected the amoeba might be attracted to a chemical called acetylcholine (ACh), which is released in large amounts by cells at the front of the brain. Ach is already known to act as a magnet for some immune cells and growing neurons.

To test this theory, Mannan looked for receptors on the amoeba that might attach to ACh. He and his colleagues started with *Acanthamoeba* – a similar genus that tends to infect people through skin wounds.

The team isolated 126 proteins from the amoeba and ran them through a database to find other proteins with similar components or structures. One of the amoeba proteins had a structure similar to the human receptor for Ach (*Journal of Receptors and Signal Transduction*, doi.org/bq29). In unpublished work, the team have repeated their search in *Naegleria* and found a similar protein.

This suggests that the amoebas have their own, ancient receptor for ACh, says Mannan. It is their attraction to the chemical that probably causes them to bypass nasal tissues and head straight for the brain.

Cabral, who was not involved in the research, agrees that ACh could be the culprit, although she would like to see more evidence to back the theory. In her own work, she has seen how the amoebas race toward brain cells in a lab dish. "It could be ACh," she says.



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On the scent

"They have these food cups on their surface, which are like giant suckers. They'll just start eating the brain"

Mannan hopes that drugs that block the receptor could offer a new treatment for the infection. Such drugs already exist, and are used for treating irritable bowel syndrome or regulating heart rate, for example. Mannan is now testing them in mice infected with the amoeba.

But there's one final hurdle to clear. If these drugs can stop the amoeba from getting into the brain, they will have to be administered as soon as a person is infected, when the condition is all but impossible to diagnose. "Severe headache is usually the first sign, but by that point the amoeba is already in the brain," says Cabral. "We need an early diagnostic test."

This could become a more urgent problem in the coming years – infections are predicted to rise as the climate warms. Jessica Hamzelou ■