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One giant step for designer babies

» **Revealed** Era of genetically modified babies moves closer, as scientists prove they can safely alter human embryos

» Inherited diseases caused by defective genes can be corrected in the earliest stage of life, revolutionary technique shows

» Same technology could be used to select stronger muscles or better eyesight, prompting fierce ethical debate

» 'They've done it. The quality of the work is high,' top scientist tells i

» Religious organisations likely to oppose groundbreaking research

SPECIAL REPORT BY STEVE CONNOR, PAGES 6-7

WORLD EXCLUSIVE

Human embryos genetically altered for first time with new technology

US scientists demonstrate how inherited diseases can be 'corrected' in early life. By **Steve Connor**

A brave new world of genetically modified "designer" babies has come a step closer with the first in-depth study showing that it is technically possible to alter the genes of human IVF embryos safely.

Scientists in the United States have for the first time convincingly demonstrated how inherited diseases caused by defective genes can be corrected in the earliest stage of life using a revolutionary gene-editing technology known as Crispr-Cas9 – likened to the "find and replace" command of word-processing software.

The same technology could, in theory, be used to enhance the genes of IVF embryos with perceived beneficial traits, such as better eyesight or stronger muscles.

However, this aspect of the research is highly controversial and will be opposed by many religious and ethical organisations.

The study was carried out on spare human eggs and donated sperm collected for research purposes by a fertility clinic at the Oregon Health and Science University in Portland. It was led by Dr Shoukhrat Mitalipov, a world authority on embryo research with a list of scientific "firsts" to his name.

Although Dr Mitalipov and his colleagues are under a strict confidentiality agreement with a leading scientific journal, which has scheduled to publish the work next month, we understand from other sources that the study breaks new ground in demonstrating the feasibility of creating genetically modified babies.

"I've heard Mitalipov has done it. He's successfully done genetic modification of human embryos. The quality of the work was high," said one senior scientist who wished to remain anonymous.

Three previous attempts at using Crispr to create genetically modified human embryos were carried out in China but produced mixed results.

The first two studies deliberately used genetically defective embryos which could not develop in the womb, but the gene editing proved highly ineffective.

The last study, published in June, involved just six normal IVF embryos created for research purposes with sperm from men carrying inherited disease genes.

Although Crispr seemed to work in correcting the disease mutation in one or two embryos, few scientists were convinced that the study showed Crispr would ever be safe enough to use in a clinical trial.

However, Dr Mitalipov's work is understood to be in a different league altogether. It was far more extensive and detailed and involved scores of embryos which were followed up with in-depth tests on the cells of each two- or three-day-old embryo to see if they were correctly edited by Crispr to eliminate the inherited disease completely.

None of the embryos was allowed to live beyond a few days in the laboratory and there was never any intention of transferring any of them into a woman's womb, which would be illegal in the US.

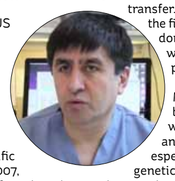
In the US state of Oregon, however, it is not illegal to create human embryos for research purposes providing the work does not involve the use of federal-government funding.

"So far as I know this will be the first study [on editing human IVF embryos] reported in the US," said Jun Wu, a researcher at the Gene Expression Laboratory of the Salk Institute for Biological Sciences in La Jolla, California, who is understood to be one of the many authors named on the paper.

Dr Mitalipov declined to comment, saying that the work is "under an embargo" until it is published.

In fact, the journal in question has yet to issue a media embargo notice on this study.

Shoukhrat Mitalipov Pioneering biologist



Born in Kazakhstan in 1961, Shoukhrat Mitalipov trained at a prestigious biological research institute in Moscow.

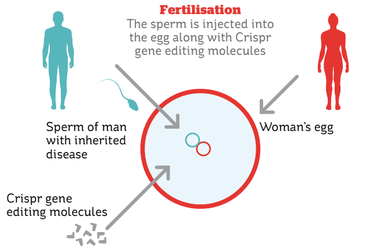
He emigrated to the US in the mid-1990s and since then has created shockwaves around the world with his repeated prowess in the manipulation of stem cells, eggs and embryos.

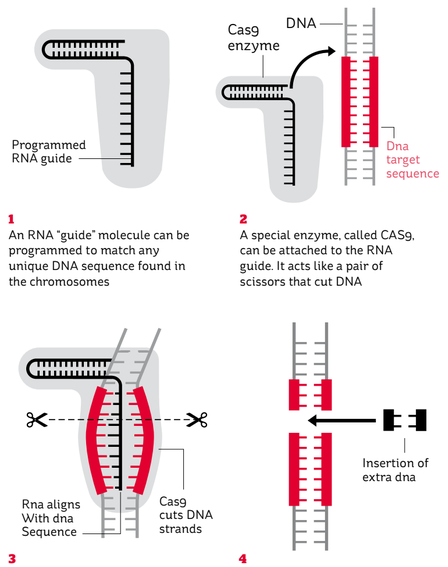
He has a list of scientific "firsts" to his name. In 2007, he unveiled the world's first cloned monkeys and in 2013 he and his team created patient-specific embryonic stem cells through the cloning of skin cells using somatic cell nuclear transfer. He has also pioneered the field of mitochondrial donation, creating the world's first "three-parent" monkeys.

However, until now Dr Mitalipov *(inset)* has not been widely known to be working on Crispr-Cas9 and human IVF embryos, especially for germline genetic engineering. That is about to change with his latest, soon-to-be-published, study.

How to create a genetically modified baby

Scientists make a dramatic breakthrough in germline genetic engineering to eliminate inherited diseases from children and all subsequent generations of their offspring





History of IVF

1930s In vitro ("in glass") fertilisation, or IVF research, began on animals in the US and other countries.

1953 American scientists extract the first intact fertilised egg.

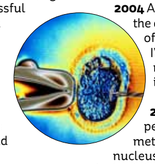
1959 US scientist Min Chueh Chang carries out the first successful IVF procedure on a rabbit.

1960s Surgeon Patrick Steptoe and Cambridge University physiologist Robert Edwards begin working together on developing lab conditions for human fertilisation and early embryo growth.

1977 Lesley Brown undergoes a procedure, now known as IVF, in November.

1978 Louise Brown is born at Oldham General Hospital, Greater Manchester on 25 July, the first ever human birth as a result of IVF.

1979 Alastair MacDonald is born in January – the world's second IVF baby and first male.



2004 Adriana Iliescu becomes the oldest woman at the age of 66 to give birth using IVF using a donated egg, a record which was passed in 2006.

2007 Shoukrat Mitalipov perfects controversial method of removing the nucleus from a human egg and placing it into another.

2010 Robert Edwards was awarded the Nobel Prize in Physiology or Medicine "for the development of in vitro fertilisation".

BACKGROUND

Technique could open the door to 'pick-and-choose' designer babies

By Steve Connor

Altering the genes of a one-day old human embryo – a single-cell "zygote" formed by the fusion of sperm and egg – is one of the most momentous operations that any medical scientist can perform.

It means an inherited disease mutation can be eliminated from all subsequent generations of any child born by the procedure, known as germline genetic engineering. It means none of their own children or grandchildren needs to suffer from the genetic disorder that plagued their ancestors.

But it also means that the same technology could be used to enhance the genes that children inherit from their parents; stronger muscles, perhaps, or keener eyesight. It opens the door to the "pick-and-choose" future of designer babies genetically engineered with desirable traits, fictionalised by Aldous Huxley in his 1932 novel *Brave New World*.

What Shoukhrat Mitalipov, of the Oregon Health and Science University in Portland, has achieved marks an important milestone in this direction. He has effectively and convincingly modified the genes of scores of one-day-old human IVF embryos with a powerful gene-editing tool known as Crispr-Cas9.

None of the embryos, which were created specifically for research purposes, was allowed to live beyond a few days in the laboratory and there was never any intention of implanting any of them into a woman's womb, which is illegal both in the United States and in Britain.

However, if what we have reported today is confirmed when Dr Mitalipov's full study is published in a leading scientific journal in the coming weeks, it will finally explode the myth that human germline genetic engineering will never be technically possible or safe enough for use in IVF clinics.

One of the important goals of Dr Mitalipov's work was to see how effective Crispr-Cas9 can be when editing out a harmful disease mutation. We understand that he created many tens of embryos using the sperm of men carrying inherited disease genes, such as sickle-cell anaemia or cystic fibrosis.

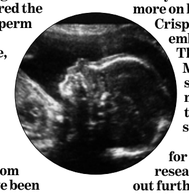
What was important was to get the Crispr-Cas9 molecules inside the fertilised egg early enough for it to do its editing work on mutated disease genes before the single-cell zygote had a chance to divide. This was critical to avoid something called mosaicism, when only some of the cells of an embryo are genetically repaired, leaving the embryo with a mixture, or mosaic, of repaired and unrepaired cells.

"If they have come up with a solution to mosaicism, then it could be a game-changer," said one senior scientist familiar with Dr Mitalipov's work.

Another scientist who knows of the work said that Dr Mitalipov seems to have overcome mosaicism with a clever trick pioneered by a British scientist, Tony Perry, at Bath University.

Dr Mitalipov injected the Crispr-Cas9 molecules into the unfertilised egg alongside a sperm cell. This was done during a routine IVF procedure known as intracytoplasmic injection (ICSI), when the unfertilised egg is fertilised artificially with a single sperm.

We understand that the Crispr-Cas9 editing tool successfully repaired the mutation of each sperm donor's defective gene. What is more, the repair was found to have worked on all the cells in almost all the IVF embryos created for the study – only "one or two" suffered from mosaicism, we have been told.



"It is proof of principle that it can work. They significantly reduced mosaicism. I don't think it's the start of clinical trials yet, but it does take it further than anyone has done before," one scientist said.

The only previous study involving viable human IVF embryos and Crispr-Cas9 was carried out by Jianquia Liu and colleagues at the Third Affiliated Hospital in Guangzhou Medical University in China, published in June. It involved just six experimental embryos carrying mutations in the genes for the blood disease beta-thalassaemia and an inherited eating disorder known as favism.

The team injected the Crispr-Cas9 components into the one-cell zygotes. Only three of the six embryos were genetically altered by Crispr and two of them suffered from mosaicism, suggesting the gene editing did not take place fast enough before the cell divided into two.

"[Dr Mitalipov's study] is a lot more substantial than the Chinese work and it was different in that they got Crispr in earlier. They injected the Crispr components alongside the sperm during ICSI [intracytoplasmic sperm injection] before fertilisation took place," the scientist said.

Only two other groups in Europe are known to be working actively on the use of Crispr gene-editing for modifying the genes of human IVF embryos.

But both Fredrik Lanner, of the Karolinska Institute in Sweden, and Kathy Niakan, of the Francis Crick Institute in London, only want to investigate the genes involved in early embryonic development to understand the causes of miscarriage.

They are both searching for new insights into pregnancy loss, rather than Dr Mitalipov's aim of altering the defective genes behind the many thousands of inherited single-gene diseases, such as sickle-cell anaemia and cystic fibrosis.

"Kathy Niakan is focussing more on how she can use Crispr to understand embryo development. This time, [Dr Mitalipov's study] seems to be a more meaningful use of this technology," said one scientist.

The next stage for Dr Mitalipov's research will be to carry out further experiments testing the safety and efficiency of Crispr-Cas9. Ultimately, there will be a desire to carry out a clinical trial, in other words to create a genetically modified embryo that is implanted into a woman's womb and allowed to develop into a full-term "GM baby".

As things stand, laws will have to be changed in both the United States and Britain to allow this. But if scientists can show it to be safe and effective and the only route to allowing a couple to have a healthy IVF baby of their own, the clamour to change the law and permit its use will undoubtedly grow.

But then comes the next question. If Crispr-Cas9 is permitted to repair inherited diseases, could is also be used for genetic enhancements? Yet, what is seen as a genetic enhancement for one person may actually be viewed as a medical treatment by another.

Cosmetic surgery was developed initially to treat people disfigured by accidents. Now it is used as beauty aid. Could germline genetic engineering go the same way?