

## New Gene Therapy Method Tested in Human Cells ... and It Works, Researchers Report

ScienceDaily-(Oct. 24, 2012) — Oregon Health & Science University's development of a new gene therapy method to prevent certain inherited diseases has reached a significant milestone. Researchers at the university's Oregon National Primate Research Center and the OHSU Department of Obstetrics & Gynecology have successfully demonstrated their procedure in human cells. It's believed that this research, along with other efforts, will pave the way for future clinical trials in human subjects.

The research results are online Oct. 24, in the journal *Nature*. Dr. Mitalipov also will present the results of his research at the American Society for Reproductive Medicine Conference in San Diego Oct. 24

The OHSU gene therapy method was initially devised through research in nonhuman primates led by Shoukhrat Mitalipov, Ph.D., associate scientist in the Division of Reproductive & Developmental Sciences at ONPRC, Oregon Stem Cell Center and OHSU School of Medicine departments of Obstetrics and Gynecology and Molecular and Medical Genetics.

The procedure was specifically developed to prevent diseases related to gene defects in the cell mitochondria. Mitalipov's previous work was published in the August 2009 edition of *Nature*. In the current study, Mitalipov, in collaboration with Paula Amato, M.D., associate professor of obstetrics and gynecology in the OHSU Center for Women's Health, demonstrated efficacy of this therapy in human gametes and embryos.

"Cell mitochondria contain genetic material just like the cell nucleus and these genes are passed from mother to infant," explained Mitalipov. "When certain mutations in mitochondrial DNA are present, a child can be born with severe conditions, including diabetes, deafness, eye disorders, gastrointestinal disorders, heart disease, dementia and several other neurological diseases. Because mitochondrial-based

### enlarge therapy to prevent diseases passed from mother to child

More than 100 genetic diseases can be passed from mother to child because of mutated genes. Researchers at Oregon Health & Science University have developed a form of gene therapy to prevent these diseases.

#### The mitochondria

Mitochondria are the powerhouses of a cell, providing it with the energy to function. A mother's egg cell contains thousands of mitochondria, each containing its own DNA. If defective, the DNA in these cells can pass diseases from mother to child. Here's how researchers hope to use gene therapy to prevent these diseases.

#### 1 Removing mother's nucleus

The cell has two nuclei: chromosomes, which contain more than 100,000 of a person's DNA. The nucleus is removed from the mother's egg cell.

#### 2 Removing nucleus from the donor's egg

The nucleus is also removed from an egg cell donated by a donor.

#### 3 Inserting mother's nucleus in donor's egg

The nucleus removed from the mother's egg cell is inserted into the donor's egg cell. Thus, the donor's normal mitochondria replace the mother's defective mitochondria containing mutated DNA.

#### 4 Paritizing the egg

A sperm cell is injected to fertilize the egg. The cell is then implanted into the mother and develops into a healthy baby.

Source: Shoukhrat Mitalipov

Illustration of the procedure. (Credit: Image courtesy of Oregon Health & Science University)

genetic diseases are passed from one generation to the next, the risk of disease is often quite clear. The goal of this research is to develop a therapy to prevent transmission of these disease-causing gene mutations."

To conduct this research, Mitalipov and his colleagues obtained 106 human egg cells from study volunteers recruited through OHSU's Division of Fertility and Reproductive Endocrinology. The researchers then used a method developed in previous nonhuman primate studies, to transfer the nucleus from one cell to another. In effect, the researchers "swapped out" the cell cytoplasm, which contains the mitochondria. The egg cells were then fertilized to determine whether the transfer was a success and whether the cells developed normally. Upon inspection, it was demonstrated that it was possible to successfully replace mitochondrial DNA using this method.

"Using this process, we have shown that mutated DNA from the mitochondria can be replaced with healthy copies in human cells," explained Mitalipov. "While the human cells in our study were allowed to develop to the embryonic stem cell stage, this research shows that this gene therapy method may well be a viable alternative for preventing devastating diseases passed from mother to infant."

The current *Nature* paper also expanded upon the previously reported nonhuman primate work by demonstrating that the method was possible using frozen egg cells. Mitochondria were replaced in a frozen/thawed monkey egg cell, resulting in the birth of a healthy baby monkey named Chrysta.

The second portion of the study, which was completed at ONPRC, is also considered an important achievement because egg cells only remain viable for a short period of time after they are harvested from a donor. Therefore, for this therapy to be a viable option in the clinic, preservation through freezing likely is necessary so that both the donor cell and a mother's cell are viable at the time of the procedure.

While this form of therapy has yet to be approved in the United States, the United Kingdom is seriously considering its use for treating human patients at risk for mitochondria-based disease. It's believed that this most recent breakthrough, combined with earlier animal studies, will help inform that decision-making process.

Because the research involved the use of human egg cells and there are restrictions to the use of federal funding for some work in human egg cells, private funding was obtained to accomplish the work.

In addition, researchers consulted with ethicists and other experts within OHSU's Institutional Review Board and the OHSU Stem Cell Research Oversight Committee (OSCRO) prior to embarking on this research. The OSCRO reviews research involving human embryonic stem cells at OHSU to ensure that all federal and state regulations governing the conduct of stem cell research are met and that all human embryonic stem cell research is conducted in accordance with the general principles expressed in the National Academies' Guidelines for Human Embryonic Stem Cell Research. The OHSU IRB reviews biomedical and behavioral research that involves humans in order to protect the rights and welfare of the research subjects.

The human oocyte/embryo research was supported by grants from the OHSU Center for Women's Health Circle of Giving and additional private funds from OHSU as well as the Leducq Foundation and the OHSU Vice President for Research office. The nonhuman primate study was supported by grants from the National Institutes of Health.

Share this story on Facebook, Twitter, and Google:

Tachibana, et al. *Nature*, 2012; DOI: [10.1038/nature11647](https://doi.org/10.1038/nature11647)