When it comes to defying the expectations of the global scientific community, few research programs can rival the Oregon Health & Science University Center for Embryonic Cell and Gene Therapy. Under the direction of Shoukhat Mitalipov, Ph.D., and with the clinical partnership of Paula Amato, M.D., the Center has made a series of discoveries that have transformed the field of reproductive biology and brought new hope to people around the globe.

Generating eggs from skin cells to treat infertility

Transplanting skin-cell nuclei into donor eggs

Infertility is a global health issue affecting millions of people worldwide. World Health Organization data suggests that between 48 million couples and 186 million individuals globally have infertility. According to the CDC, about 1 in 5 women in the U.S. are unable to become pregnant. To help address this important problem, the Center developed a first-of-its-kind method to turn an individual's skin cell into an egg with the potential to produce viable embryos and live offspring. The technique, developed and verified in mice, provides new hope for women experiencing age-related decline in fertility, patients whose fertility has been compromised by cancer treatment, and same-sex male couples who wish to have a child genetically related to both partners.
Significant scientific, ethical, and regulatory challenges must be addressed before this technology moves into human clinical trials. These challenges are exacerbated by the fact that women’s health research is woefully underfunded and the fact that federal funding for human embryo research is prohibited. In 2022, Open Philanthropy provided a grant of $4 million over three years to enable the next step of conducting proof-of-concept studies in vitro with human eggs and sperm. These studies will deepen our understanding of mechanisms required to successfully transform skin cells into eggs, paving the way for global clinical trials in the next few years.

**Treating degenerative diseases**

**Horizontal mitochondrial DNA exchange**

Mitochondria within a cell are unique in many respects. They are crucial to generating energy in the body and carry their own mitochondrial DNA (mtDNA). Mitochondrial DNA is also particularly prone to deterioration as we age, which can lead to a variety of diseases, including Alzheimer’s and heart disease. Up until now, scientists assumed that mtDNA was transmitted exclusively from parent cell to daughter cells during cell division (vertically). But Mitalipov’s lab has shown in mice studies that these cells may actually donate and accept mitochondria from one another throughout the lifetime (horizontally), an insight that could lead to new methods for repairing damaged mitochondria and treating degenerative conditions like Alzheimer’s and Parkinson’s disease.

Recognizing the importance of this discovery, in 2019 the National Institutes of Health provided the Center a five-year grant of $3.6 million to further develop their findings. Their research will make a significant impact on our understanding of mtDNA biology and guide the development of future cures that could impact millions of people around the globe.

**Preventing transmission of mitochondrial disease**

**Mitochondrial replacement therapy**

One out of every 4,000 babies born in the U.S. inherits mutant mitochondrial DNA (mtDNA), which is linked to blindness, diabetes and many other diseases. In 2009, Mitalipov’s team demonstrated a new gene therapy technique that makes it possible for macaque monkeys with mutant mtDNA to avoid passing it along to their offspring. By 2012, they succeeded in using the new technique, called mitochondrial replacement therapy, in human embryos. The technique involves transferring the mother’s nuclear DNA (spindle) into a donor egg with healthy mitochondria.

Scientists are now testing this technique’s potential in human clinical trials in Europe, since such studies are currently prohibited in the U.S. Recent research

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“I see patients and families every day who desperately need these technologies. If these techniques prove safe and effective, then many generations will benefit. We’re eternally grateful to our forward-looking philanthropic partners who make it possible to see these ideas through.”

Paula Amato, M.D., professor of obstetrics and gynecology and director, Division of Reproductive Endocrinology and Infertility School of Medicine
suggests that in some cases the damaged mtDNA may reassert itself as the child ages. As with all new reproductive technologies, researchers are moving forward with caution. OHSU’s Center continues to collaborate with its international partners to advance the science underpinning this clinical approach.

This same technique is also being investigated as a potential treatment for age-related female infertility.

**Preventing hereditary diseases from being passed down to future generations**

**Germline gene editing**

In 2017, Mitalipov and colleagues published groundbreaking research in *Nature* demonstrating that the gene-editing tool CRISPR can be used to repair a disease-causing gene mutation in early human embryos—and prevent the disease from being passed down to future generations. The study focused on repairing the single gene that causes hypertrophic cardiomyopathy, a common heart condition that affects 1 in 500 people. The breakthrough gives new hope to aspiring parents who carry the gene mutation, potentially allowing them to repair the damaged gene during vitro fertilization (IVF). The team believes this approach could be adapted to prevent other single-gene diseases such as cystic fibrosis, Huntington’s, and inherited cancers such as those related to the BRCA gene, just to start. There are over 10,000 diseases for which this approach could work.

This research was hailed as one of the century’s most important scientific breakthroughs in 2017, but there’s still a long way to go before the technique can be put into practice. In 2023, the team published findings suggesting that editing one gene may cause problems in other genes, highlighting the need for further study. The team is now exploring newer gene editing tools like base-editing, which may be safer.

**Replacing diseased or injured cells**

**Somatic cell nuclear transfer**

Mitalipov and his team published a study in *Cell* in 2013 that described a new process for converting human skin cells to embryonic stem cells. The process, referred to as SCNT (somatic cell nuclear transfer), replaces the nucleus in an unfertilized human egg with a nucleus from a patient’s skin cell. By creating rejection-proof, genetically matched human embryonic stem cells, Mitalipov’s lab opened a promising pathway to cell- and gene-based cures. In the future, doctors may be able to use these cells to replace diseased or injured nerve, muscle, organ, bone or blood cells. OHSU is one of only a couple of institutions in the world capable of producing and testing these cells.
PAULA AMATO, M.D., is professor of obstetrics and gynecology and director of the Division of Reproductive Endocrinology and Infertility in the School of Medicine at Oregon Health & Science University. She received her medical degree from the University of Toronto in Canada, where she also completed her residency in obstetrics and gynecology, followed by a fellowship in reproductive endocrinology and infertility at the University of California, San Diego. Her research focuses on innovative assisted reproductive technologies for the treatment of infertility and ovarian aging.

SHOUKHRAT MITALIPOV, PH.D., directs the OHSU Center for Embryonic Cell and Gene Therapy. He is a professor at the Oregon National Primate Research Center with appointments at biomedical engineering, obstetrics and gynecology, and pediatrics and the Knight Cardiovascular Institute in the OHSU School of Medicine. Mitalipov was born in Almaty, Kazakhstan, and earned his Ph.D. in 1994 from the Research Center for Medical Genetics in Moscow. He arrived at OHSU in 1998 after conducting postdoctoral research in stem cell and developmental biology at Utah State University. Mitalipov holds seven U.S. patents in techniques involved in gene therapy approaches for both nuclear DNA and mitochondrial DNA.

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