Medical Xpress

A better way to deliver fetal therapy for serious genetic disorders

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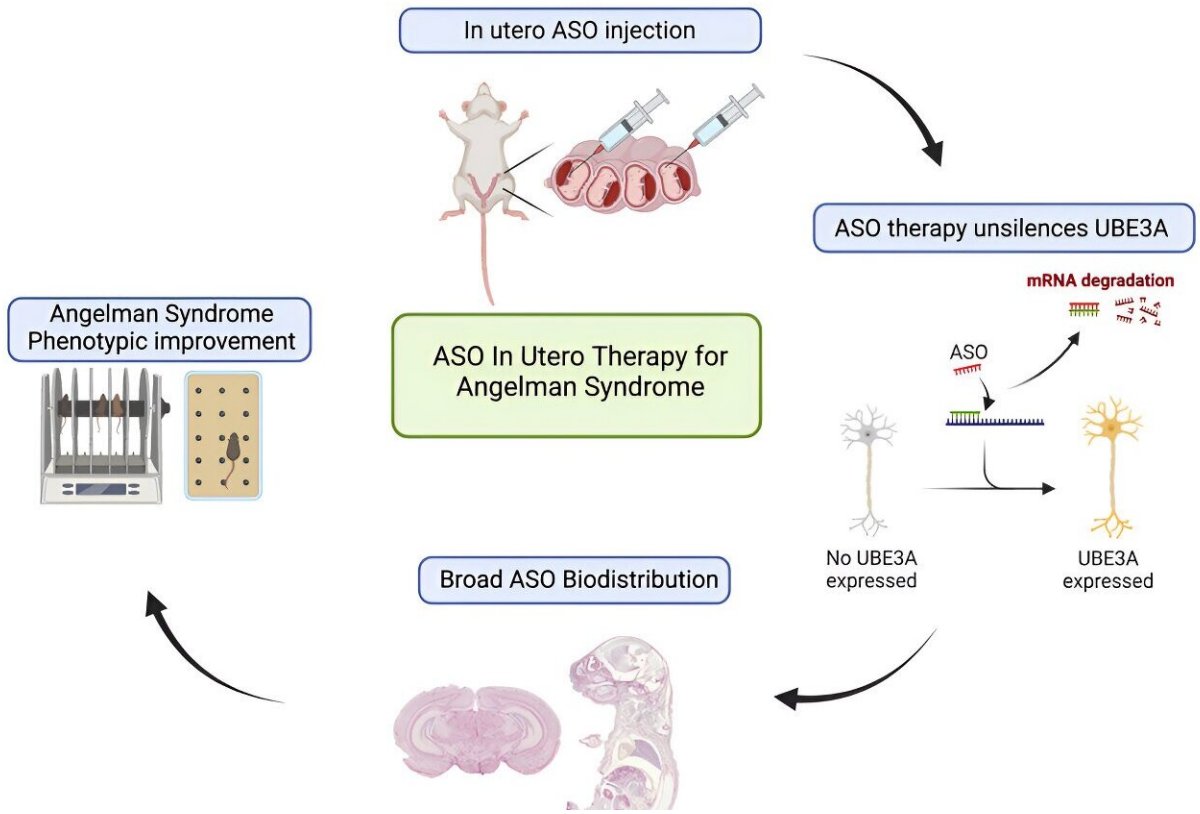

Graphical Abstract. Credit: *Molecular Therapy* (2024). DOI: 10.1016/j.ymthe.2024.02.004

In a discovery that opens the door to a less invasive way of treating some serious disorders before birth, UC San Francisco scientists have found

that delivering medicine through amniotic fluid is as effective as delivering it to the fetal brain via cerebrospinal fluid. The experiment was done in mice with a genetic disorder called Angelman syndrome.

Treating genetic diseases like Angelman in utero could prevent serious symptoms that begin while the fetus is still developing. It's also easier to access neurons in the fetal brain because the blood-brain barrier that normally acts as a filter to prevent molecules from reaching the brain is not yet fully formed.

The treatment uses therapeutic molecules called antisense oligonucleotides, or ASOs, that can alter the expression of genes through interactions with RNA, which creates proteins.

"ASOs are currently given to children with diseases affecting the nervous system," said Tippi MacKenzie, MD, a fetal and pediatric surgeon at UCSF Benioff Children's Hospitals and the senior author of the study, which appears in *Molecular Therapy*.

"However, children who have a severe version of a genetic condition may have irreversible damage by the time they are born that cannot be addressed after birth."

Previous research has shown that Angelman syndrome, a severe neurological condition marked by intellectual disabilities, seizures and abnormal gait, can be diagnosed before birth, and that expression of the part of the gene that causes the syndrome can be manipulated prenatally.

The treatment improved the motor function and learning of the mice pups after they were born. And injecting the therapy directly into the amniotic fluid allowed it to circulate into the intestines, lungs, liver, kidneys and stomach, and helped reinstate gene expression in critical parts of the brain.

"By injecting into the amniotic fluid, we could give a much higher dose than when we injected into the cerebrospinal fluid," MacKenzie said. "Injecting this way also created a more 'slow release' approach."

The researchers hope this will enable them to treat conditions such as pulmonary hypertension and cystic fibrosis prenatally.

"Both types of prenatal injections we tried, into the cerebrospinal fluid and into the amniotic fluid, allowed the therapy to penetrate deep regions of the brain that are critical areas to treat for Angelman Syndrome," said Maria Clark, B.S., a UCSF research associate in MacKenzie's lab. "This is a big hurdle to overcome when treating genetic conditions of the nervous system."

The team is now working with a large animal model to determine whether ASOs delivered into the amniotic fluid can cross into the brain and spinal cord as well as they did in mice. They are also speaking to parents whose children are affected by Angelman syndrome and related disorders to understand their perspectives on seeking prenatal therapy.

More information: Maria T. Clarke et al, Prenatal delivery of a therapeutic antisense oligonucleotide achieves broad biodistribution in the brain and ameliorates Angelman syndrome phenotype in mice, *Molecular Therapy* (2024). DOI: 10.1016/j.ymthe.2024.02.004

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