

# **In-utero treatment reverses cleft palate in mice**

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In a Pax9<sup>+/+</sup> embryo at E18.5, normal palatal fusion with parallel rugae arrangement is visible. Credit: Rena D'Souza

Researchers at University of Utah Health clarified a molecular pathway responsible for the formation of cleft palate and identified a new treatment to reverse this defect in mouse pups in-utero. These findings, published on September 5 in the journal *Development*, offer a new way to think about cleft development and could potentially yield treatments to prevent this common birth defect in people.

"As a clinician, I understand the devastating consequences of [cleft palate](#)," said [Rena D'Souza, D.D.S., Ph.D.](#), professor of Dentistry at U of U Health.

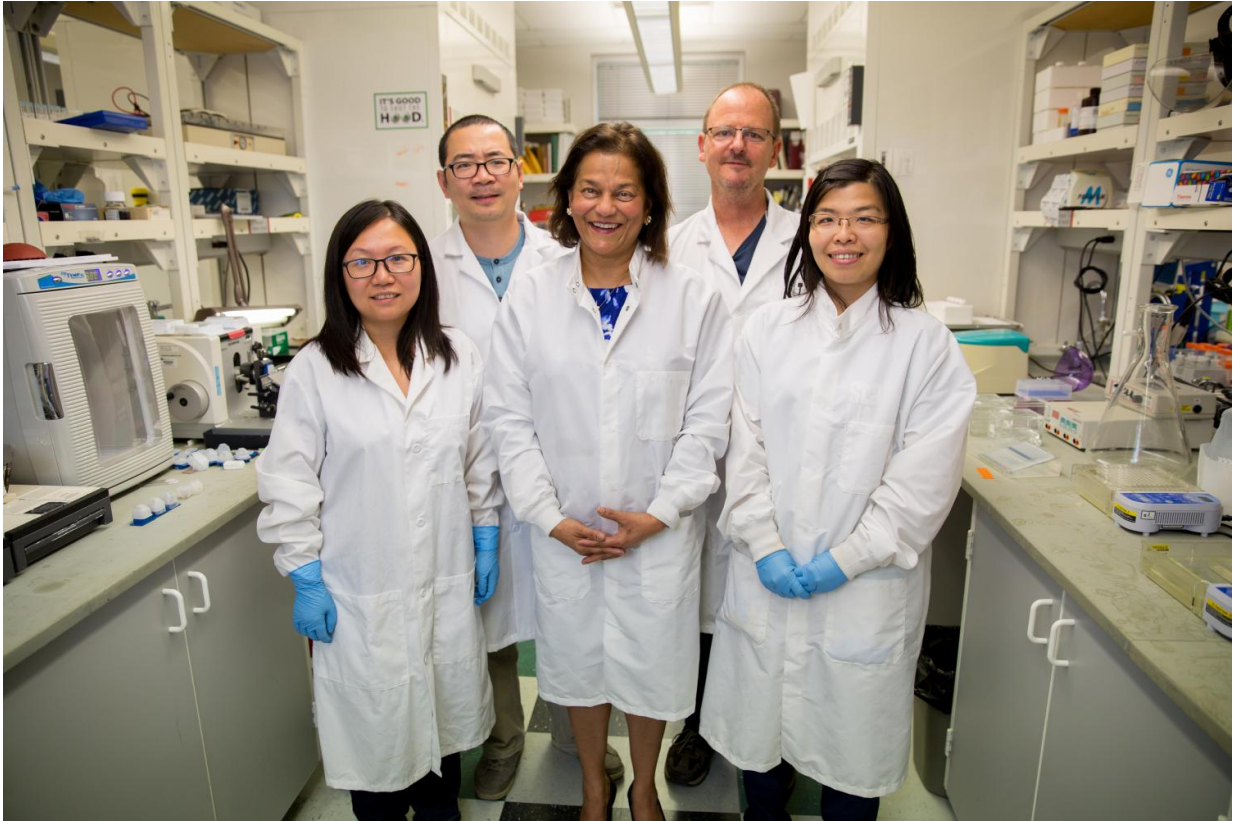
Cleft palate is one of the most common birth defects, affecting [6 in 2,651](#) children born in the United States. The [cleft](#) forms when the bony tissue covering the roof of the mouth fails to join during pregnancy. Children with a cleft palate require reconstructive surgery and complex life-long treatments.

D'Souza and her team originally set out to investigate a different tissue: teeth. Using mice as a model, they had planned to clarify the role of two sets of [genes](#) - PAX 9 and Wnt genes - in regulating tooth formation. Unexpectedly, their work revealed how the interplay between these two genes at a critical window of development is needed for the palatal shelves to grow and fuse in the midline.

"It was really serendipitous," she said. "For the first time, we can show the involvement of the Wnt pathway during palate fusion."

Like people born with a cleft palate, the two sides of the palate fail to fuse in mice lacking the gene PAX9. At the molecular level, D'Souza found another abnormality. The mice missing this gene had an increase in two genes, called Dkk1 and Dkk2, that block the Wnt signaling

pathway.



D'Souza research team. Credit: University of Utah Health

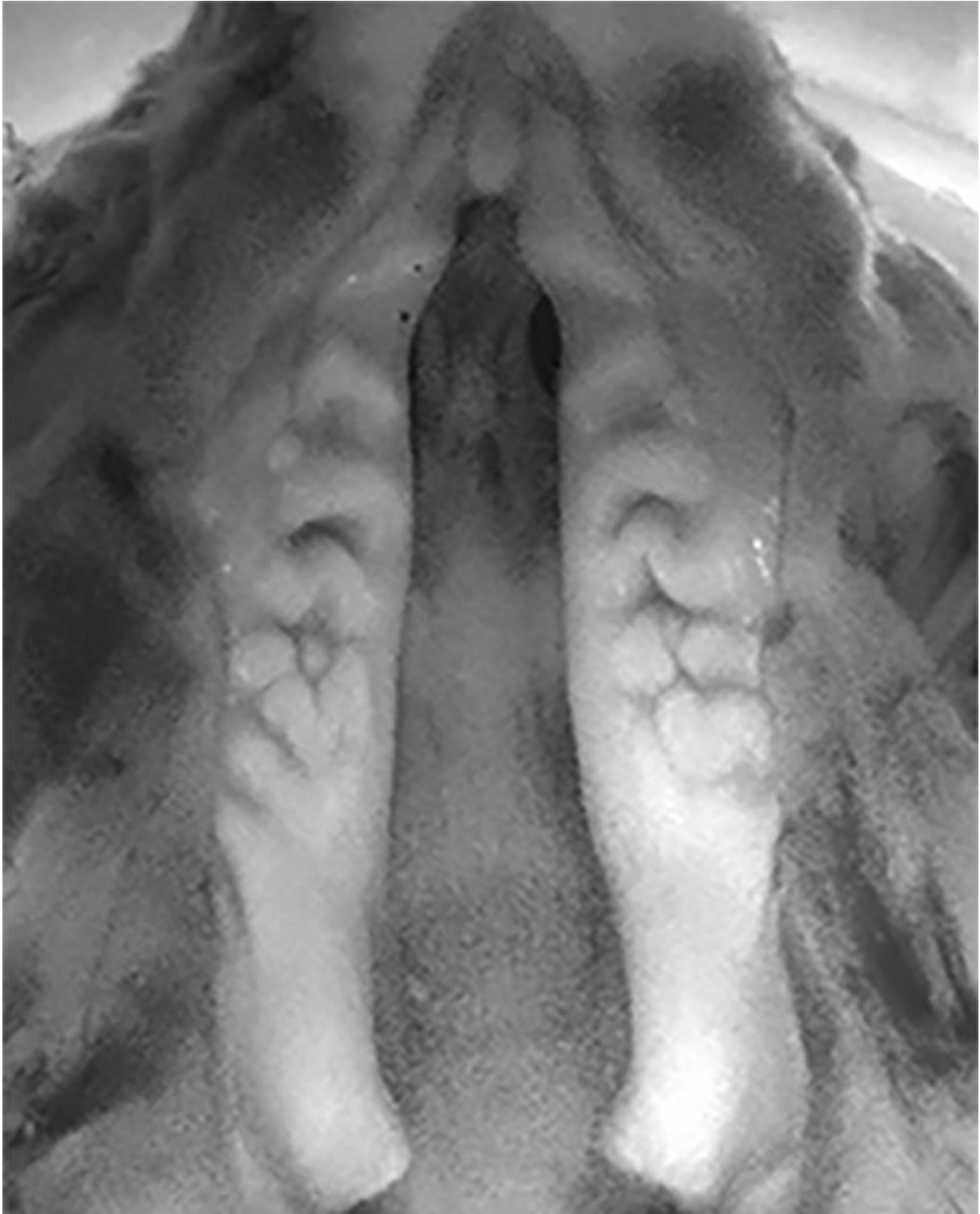
D'Souza attempted to rectify that change by administering a pharmacological Wnt-based treatment that inhibited Dkk (WAY-262611) intravenously through the mother rat's tail vein during a critical window of the pups' gestation, when palate formation is initiated and ongoing.

Treatment restored palate fusion in all of the pups tested. The drug works by blocking the Dkk genes and restoring the Wnt pathway.

The researchers found no adverse health effects after monitoring the mother mice and their pups exposed to the treatment for 18-months.

Along with cleft defects, PAX9-deficient pups also experience defects in their hind limb, as well as parathyroid and thymus glands. The Wnt-based treatment did not prevent the other defects, and the PAX9-deficient pups soon died after birth. D'Souza believes the premature death is more likely related to abnormal calcium levels, contrary to previous claims that early death was due to malformed palate.

D'Souza acknowledges that more work is necessary to ensure the Wnt-based therapy does not affect other organ systems negatively or produce long-term health problems.



Cleft palate in a Pax9<sup>-/-</sup> embryo. Credit: Rena D'Souza

"These seminal findings are exciting for the field, because Dr. D'Souza and her team have opened an interesting door into potential pharmacological therapies," said Ophir Klein, M.D., Ph.D., Chief of Genetics at the University of California San Francisco. Klein, who is not an author on the study, believes it presents a new strategy for the [treatment](#) of single-gene disorders in humans, which can be exploited for new approaches to reverse these defects in humans.

D'Souza believes these findings offer some babies born with cleft palate something that was missing before, hope.

"Clearly, there is more work to be done prior to implementation for humans, but it seems feasible to translate this research into Wnt-based treatments for people," she said. Future work is necessary to investigate if it is safe and effective to deliver a drug to human babies in-utero or directly to newborns with palate defects.

**More information:** Shihai Jia et al, Small-molecule Wnt agonists correct cleft palates in Pax9 mutant mice in utero, *Development* (2017). [DOI: 10.1242/dev.157750](https://doi.org/10.1242/dev.157750)

Provided by University of Utah Health

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