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Trainor Lab prevents rare birth defect by inactivating p53 gene

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Using a mouse model of Treacher Collins Syndrome (TCS), the Stowers Institute's Trainor Lab has demonstrated that it can prevent this rare disorder of craniofacial development either by inactivating a gene implicated in the abnormality or by inhibiting its protein product.

The work, which was posted to the Web site of the journal *Nature Medicine* yesterday, is a follow-up to the team's 2006 discovery of the cellular cause of TCS.

The team evaluated how a mutated TCOF1 gene causes the death of neural crest cells that should otherwise form most of the bone, cartilage, and connective tissue that make up the head and face during embryonic development. The loss of these cells results in abnormal development of the ear, nose, and upper and lower jaw, including cleft palate.

The team discovered that chemical inhibition of a single protein, the product of the p53 gene, could prevent the craniofacial abnormalities caused by the TCOF1 mutation. They also showed that inactivation of the p53 gene itself enabled neural crest cells to survive and form normal craniofacial structures in embryos carrying the TCOF1 mutation.

"Inhibition of the p53 protein was enough to prevent neural crest cells from dying during early embryogenesis and essentially rescue the mouse embryo from the devastating craniofacial features associated with TCS," said Natalie Jones, Ph.D., formerly a Postdoctoral Research Associate in the Trainor Lab and first author on the paper. "The successful rescue of

neural crest cell development in a congenital craniofacial anomaly such as TCS is exciting because it provides an attractive model for the prevention of other craniofacial birth defects of similar origins."

"These findings are the culmination of years of efforts to better understand TCS," said Paul Trainor, Ph.D., Associate Investigator and senior author on the paper. "People diagnosed with severe TCS typically undergo multiple, major reconstructive surgeries that are rarely fully corrective. The inhibition of p53 brings us much closer to our ultimate goal — preventing TCS and the suffering it causes altogether."

"By its very nature, the progress of basic biomedical research is incremental," said Robb Krumlauf, Ph.D., Scientific Director. "We learn a little bit at a time over many years, and each new discovery contributes to a more comprehensive understanding of a disease. This discovery by the Trainor Lab is what all of those years of hard work are about — ultimately learning enough to treat, cure, or prevent a devastating disease."

"These meticulously performed experiments by members of the Trainor Lab and their colleagues elegantly demonstrate the power of science to address the cause and prevention of birth defects," said William Neaves, Ph.D., President and CEO. "All of us at the Stowers Institute celebrate their landmark accomplishment."

Source: Stowers Institute for Medical Research