Researchers detail groundbreaking Angelman syndrome development

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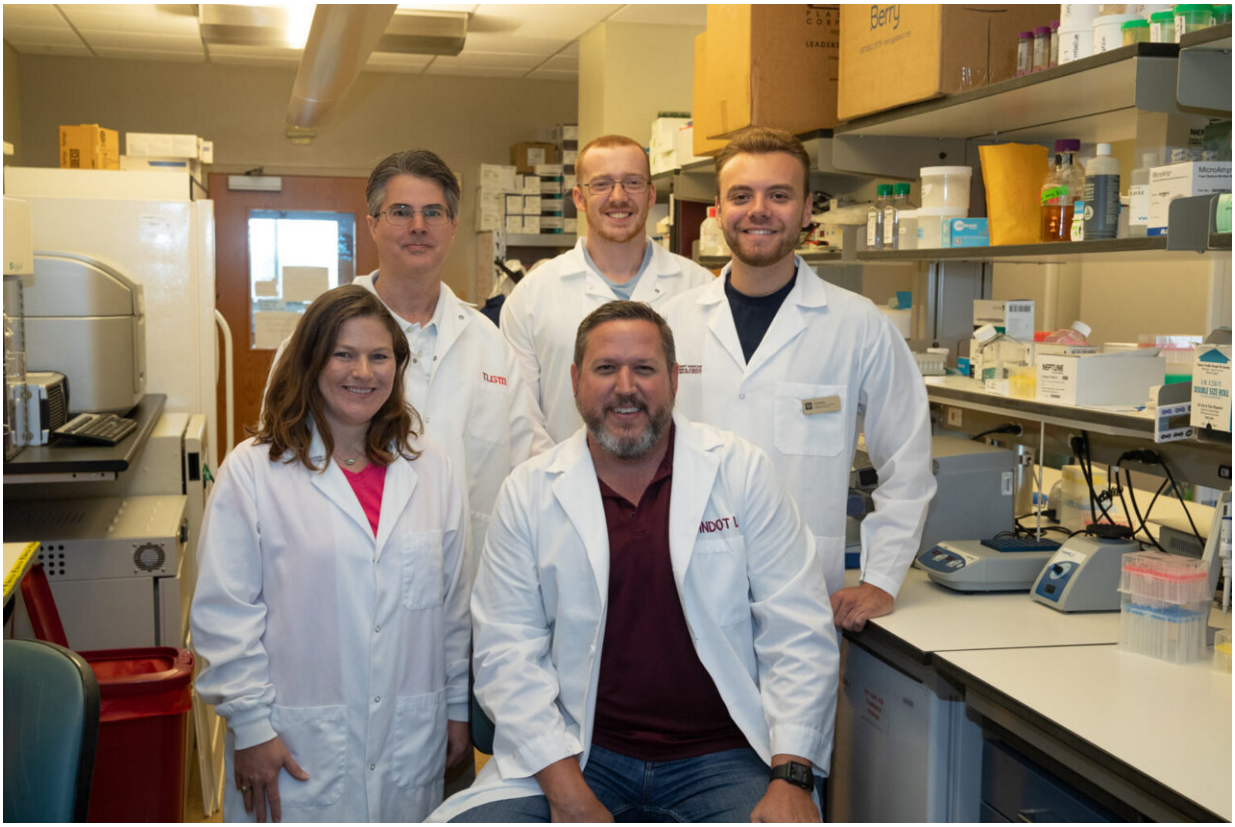

The Dindot Lab team, including Dr. Scott Dindot (front right); Dr. Sarah Christian (front left); (back row, l-r) Dr. Johnathan Ballard, Texas A&M Institute for Genomic Medicine; and biomedical sciences doctoral students Luke Myers and Tom Jepp. Credit: Texas A&M School of Veterinary Medicine & Biomedical Sciences

Researchers at Texas A&M University have developed the first molecular therapeutic for Angelman syndrome to advance into clinical development.

In a new article, published today in *Science Translational Medicine*, Dr. Scott Dindot, an associate professor and EDGES Fellow in the Texas A&M School of Veterinary Medicine and Biomedical Sciences' (VMBS) Department of Veterinary Pathobiology, and his team share the process through which they developed this novel therapeutic candidate, also known as 4.4.PS.L, or GTX-102. Dindot is also the executive director of molecular genetics at Ultragenyx, which is leading the development of GTX-102.

Angelman syndrome (AS) is a devastating, rare neurogenetic disorder that affects approximately 1 in 15,000 live births per year; the disorder is triggered by a loss of function of the maternal *UBE3A* gene in the brain, causing developmental delay, absent speech, movement or balance disorder, and seizures.

There are no approved therapies for AS, and the current standard of care is focused on behavioral therapy and controlling specific symptoms, specifically the seizures that often affect patients with AS.

In healthy individuals, the copy of the *UBE3A* gene inherited from the mother is expressed in the brain and the copy of the *UBE3A* gene inherited from the father is turned off by another gene, called the *UBE3A* antisense (*UBE3A-AS*) transcript. Individuals living with AS have mutations that affect the expression or function of the maternal copy of *UBE3A* and, as a result, they lack the *UBE3A* protein in their brain. Dindot and his team began their research looking for a way to prevent the silencing of the paternal *UBE3A* gene and reactivate expression of the deficient protein.

In their research, Dindot and his team used different genomic approaches to understand how the *UBE3A-AS* transcript is regulated in the brain. Their work uncovered a previously unknown region in *UBE3A-AS* that they believe represents the ancestral origin of the gene in mammals. They also believe this region plays a key role in regulating the expression of *UBE3A-AS*.

"Parts of this region have remained unchanged for over 30 million years," Dindot said. "The *UBE3A-AS* transcript is an incredibly complex gene. What it is and how it is regulated has been debated for years."

The team then developed antisense oligonucleotides (ASOs)—small synthetic molecules comprising DNA and RNA—to target the conserved region in the *UBE3A-AS* transcript. ASO drugs work by binding to a target RNA and cutting it, causing the gene to stop making the RNA.

The team found that ASOs targeting the conserved region effectively turned off *UBE3A-AS*, which, in turn, reactivated the expression of the paternal *UBE3A* allele. The studies show that the ASOs reactivated the expression of the paternal *UBE3A* allele and increased *UBE3A* protein in cultured neurons from individuals with AS.

As a result of this research, Dindot developed the lead compound referred to as GTX-102, which is now in clinical development.

"We used a novel approach to designing the ASOs, targeting a very specific part of a gene rather than just giving a drug to treat a symptom," Dindot said. "In theory, this treatment goes after the heart of the condition."

Interim data from a phase 1/2 clinical trial of GTX-102 in the United States, United Kingdom and Canada have previously indicated that the compound has demonstrated "meaningful improvement" in pediatric

patients afflicted with AS.

"Moving forward, our research and findings not only offer promise for AS but also provide a path forward for developing ASO therapies for other genetic disorders," Dindot said.

More information: Scott V. Dindot et al, An ASO therapy for Angelman syndrome that targets an evolutionarily conserved region at the start of the UBE3A-AS transcript, *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.abf4077

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