

These data suggest that in patients with STEMI and intermediate disease in nonculprit coronary-artery lesions, a more deliberate approach with noninvasive assessment of ischemia results in a lower number of patients undergoing PCI than with iFR-guided evaluation, with similar outcomes. The nonculprit coronary-artery stenosis in the patients enrolled in this trial appears to have been less severe than that in the patients in the earlier COMPLETE trial, in which more than 99% of the nonculprit coronary lesions had more than 70% stenosis.<sup>1</sup> It may be that more severe nonculprit lesions cannot be safely deferred, because the chance for spontaneous myocardial infarction is more likely in severe lesions, especially if the FFR is abnormal.<sup>9</sup> Until we have more data, guidelines recommend that patients in hemodynamically stable condition with STEMI and severe nonculprit lesions should continue to undergo early angiography-guided complete revascularization, whereas those with less severe nonculprit lesions can undergo a more deliberate ischemia-guided approach.<sup>10</sup>

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

<sup>1</sup>Division of Cardiovascular Medicine, Stanford University, Stanford, CA; <sup>2</sup>Stanford Cardiovascular Institute, Stanford University, Stanford, CA; <sup>3</sup>Veterans Affairs Palo Alto Health Care System, Palo Alto, CA.

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## SCIENCE BEHIND THE STUDY

# Toward a Disease-Modifying Therapy for Dravet Syndrome

Gemma L. Carvill, Ph.D.,<sup>1</sup> and Heather C. Mefford, M.D., Ph.D.<sup>2</sup>

**I**n this issue of the *Journal*, Laux et al.<sup>1</sup> report the results of two phase 1–2a, open-label trials investigating the effects of zorevunersen, an **anti-sense oligonucleotide** (see Key Concepts) that rescues **SCN1A haploinsufficiency** by preventing the inclusion of a poison exon, as a potential disease-modifying therapy for Dravet syndrome. Although preliminary, these results are consistent with a therapeutic effect.

### WHAT IS DRAVET SYNDROME?

Dravet syndrome, first described by Dr. Charlotte Dravet in 1978, is a developmental and epileptic encephalopathy.<sup>2</sup> Although the syndrome is char-

acterized by phenotypic variability, affected persons typically present with prolonged febrile seizures before 1 year of age, with additional seizure types emerging over time along with developmental delays affecting cognition, speech, and motor development. With an estimated incidence of 1 in 15,700 persons, Dravet syndrome is a rare disease<sup>3</sup>; however, among the developmental and epileptic encephalopathies, it is the most commonly diagnosed and well-studied.

### WHAT CAUSES DRAVET SYNDROME?

Dravet syndrome is caused by heterozygous, **loss-of-function variants** in the gene **SCN1A**, which

encodes a sodium channel type 1 alpha subunit ( $\text{Na}_v1.1$ ) that regulates neuronal excitability. The *SCN1A* variants that cause Dravet syndrome usually occur spontaneously — that is, they are **de novo variants**. More than 1000 distinct *SCN1A* pathogenic variants that result in loss of function of the  $\text{Na}_v1.1$  protein have been identified, including deletion, nonsense, frameshift, and missense variants. The second allele of *SCN1A* remains intact, but a single working copy of *SCN1A* is not sufficient to maintain a healthy state, which makes Dravet syndrome a disease due to haploinsufficiency.

#### WHAT ARE POISON EXONS?

Poison exons, also referred to as **nonsense-mediated mRNA decay (NMD)** or nonproductive exons, are naturally occurring, alternatively spliced exons present in roughly a third of genes in the genome. When spliced into a messenger RNA (mRNA) transcript, poison exons introduce a premature stop codon, leading to NMD of the resulting transcript and no subsequent protein production (Fig. 1). *SCN1A* contains a poison exon (called 20N) between exons 20 and 21. In mice and humans, 20N is preferentially included early in neurodevelopment when  $\text{Na}_v1.1$  is not needed; the 20N exon is increasingly skipped with advancing gestational age.<sup>4,5</sup> Postnatally, a small fraction of *SCN1A* transcripts include the poison exon. The regulation of inclusion (or exclusion) of 20N (through **alternative splicing**) is thought to modulate  $\text{Na}_v1.1$  protein levels across stages of development; disruption of this regulation can cause disease. For example, variants in *SCN1A* that lead to increased incorporation of the 20N exon are associated with Dravet syndrome and related phenotypes.<sup>6</sup> Conversely, preventing the inclusion of a poison exon can increase the production of full-length protein by diminishing the pool of nonfunctional “poisoned” *SCN1A* mRNAs and increasing the pool of full-length *SCN1A* mRNAs. The latter approach was used by Laux et al.

#### THERAPEUTIC APPROACHES

Treatment for Dravet syndrome includes standard antiseizure medications to control seizures and developmental or behavioral therapies for the related developmental phenotypes. However, these interventions are not disease-modifying. Patients continue to have seizures and developmental delays and have a high risk of sudden



#### Alternative splicing

Use of different exons in the formation of messenger RNA (mRNA) from initially identical transcripts, which can result in the generation of related proteins from one gene, often in a manner specific to a type of tissue or a developmental stage.

#### Antisense oligonucleotide

A short (typically 12 to 30 nucleotides) single strand of chemically modified nucleotides that target mRNA to prevent translation into protein. Antisense oligonucleotides can bind directly to mRNA, leading to mRNA degradation; can inhibit generation of mature mRNA by blocking splicing of precursor forms of mRNA; or can block ribosome recruitment to inhibit protein translation. Antisense oligonucleotides can also be designed to target other RNAs, such as microRNAs and long noncoding RNAs.

#### Haploinsufficiency

A state in which a loss-of-function variant affecting one allele in a diploid organism results in the expression of only 50% the normal active form of a particular protein. The loss of half the protein activity is sufficient to cause disease.

#### Nonsense-mediated mRNA decay (NMD)

The process by which cells recognize and degrade mRNA that contains frameshift or nonsense variants. The net effect of this mechanism is to rid the cell of mRNA that is unlikely to encode a functionally useful protein.



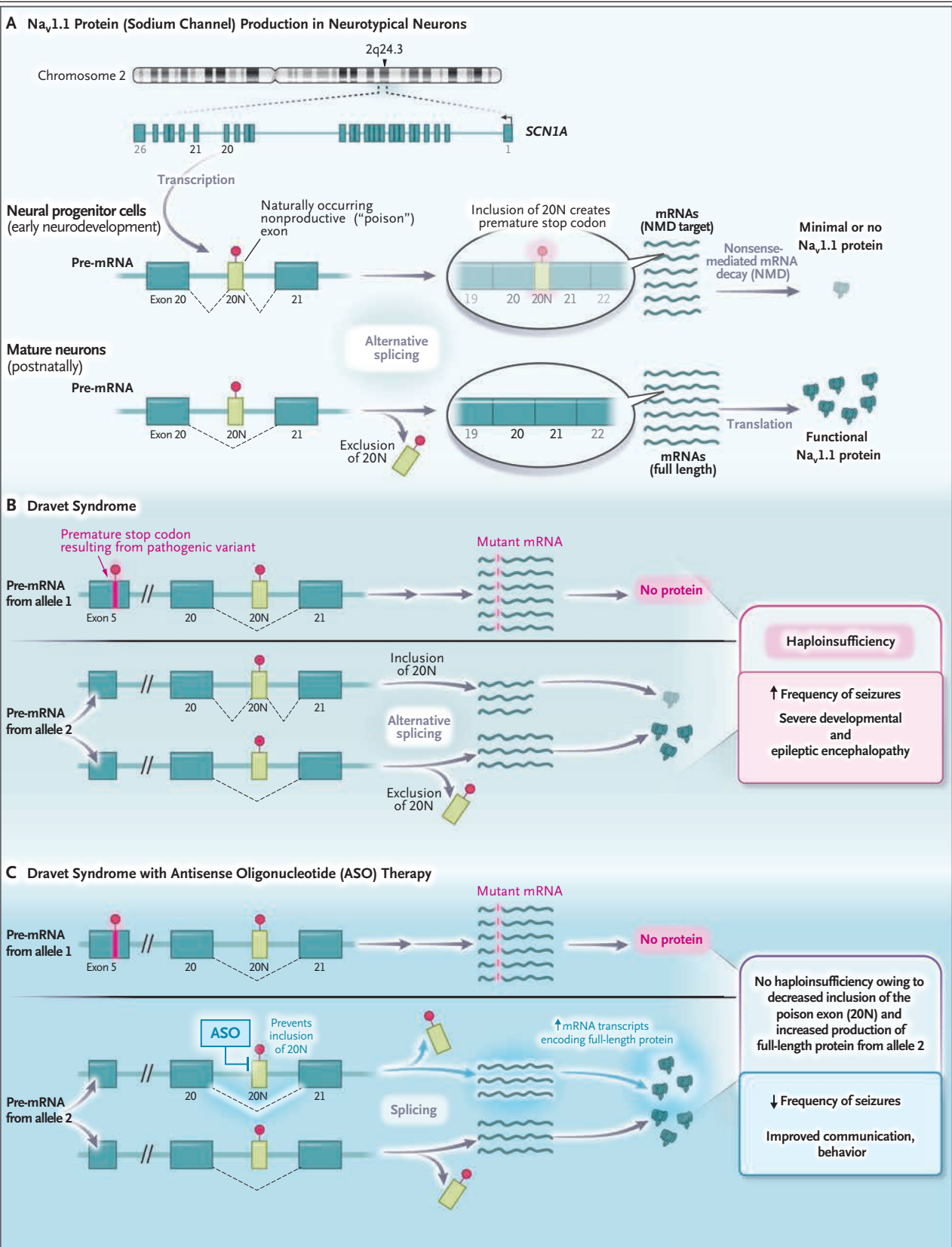
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unexplained death in epilepsy (SUDEP), even when antiseizure medications decrease seizure frequency. Rather than treatment of the symptoms of the disorder (seizures), therapeutic strategies are needed to rescue haploinsufficiency and restore physiologic  $\text{Na}_v1.1$  levels.

#### WHAT IS ZOREVUNERSEN?

Antisense oligonucleotides are short (approximately 20 bp) DNA molecules that are designed to target a specific RNA transcript on the basis of sequence. Depending on the specific design and chemistry, they alter the abundance or splicing of an mRNA transcript. Zorevunersen is a



**Figure 1 (facing page). Targeting a “Poison” (Nonproductive) Exon to Treat Dravet Syndrome.**

*SCN1A* contains a poison exon (called 20N) between protein-coding exons 20 and 21. When the poison exon is skipped, as is typically the case with advancing gestational age, the resulting transcript is translated to a full-length, functional Na<sub>v</sub>1.1 protein (Panel A). Because the poison exon contains a stop codon, its inclusion (which occurs through alternative splicing) results in nonsense-mediated mRNA decay (NMD) and diminished levels of functional Na<sub>v</sub>1.1. Dravet syndrome (Panel B) occurs when one allele of *SCN1A* has a pathogenic variant that leads to a nonfunctional or absent protein (allele 1); the full-length mRNA transcript produced from the wild-type allele (allele 2) is not sufficient to prevent disease. Zorevunersen (Panel C), an antisense oligonucleotide targeted to the poison exon, blocks the inclusion of 20N during alternative splicing, leading to an increase in the number of transcripts encoding full-length, functional Na<sub>v</sub>1.1 protein from the wild-type allele (allele 2). Although zorevunersen also prevents inclusion of the poison exon in RNA transcribed from allele 1, the resulting transcript contains the pathogenic stop codon, so no functional protein is produced. The results reported by Laux et al.<sup>1</sup> support a reduction in the frequency of seizures among persons with Dravet syndrome who received zorevunersen.

splice-switching antisense oligonucleotide that prevents the inclusion of exon 20N, thereby increasing levels of full-length *SCN1A* mRNA and Na<sub>v</sub>1.1 protein (Fig. 1). Because it is designed to target the naturally occurring poison exon rather than specific pathogenic variants, it should be effective for all persons with Dravet syndrome. In a preclinical mouse model of Dravet syndrome, zorevunersen (also known as STK-001) rescued seizure phenotypes and prevented SUDEP.<sup>7</sup>

Although the results reported by Laux et al. are preliminary, they support a reduction in the median frequency of convulsive seizures by up to 80% at the highest dose — a reduction that would be unprecedented if borne out by the final results. Moreover, their early results support

improvements in communication, adaptive behavior, and quality-of-life indexes in the participants, whose ages ranged from 2 to 18 years.

**WHAT'S NEXT?**

Many disorders due to haploinsufficiency are linked to genes that contain poison exons; the splice-switching antisense oligonucleotide approach used by Laux et al. could therefore be more broadly applicable. In theory, the inverse strategy, involving the forced inclusion of a normally excised poison exon, could potentially be used to treat disorders caused by gain-of-function variants. In the meantime, the results of ongoing trials of zorevunersen in Dravet syndrome are eagerly awaited.

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<sup>1</sup>Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago; <sup>2</sup>Center for Pediatric Neurological Disease Research, Department of Cell and Molecular Biology, St. Jude Children's Research Hospital, Memphis, TN.

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