Treating Genetic Causes of Dravet Syndrome

In September 2014, identical twins Hudson Blake and Grady Lee were born and appeared seemingly perfect. However, when their mom went to return to work when the boys were 12 weeks old, she started to notice they both had an odd shiver. When Hudson began shivering again one day, his mom took him to the ER, where he started having another episode, and it was confirmed as a seizure. One week later, Grady had a similar seizure and was admitted to the ER. The family says the following year was a roller coaster of different medications and constant hospitalizations. As the boys grew and met milestones, doctors assured the parents that Hudson and Grady would grow out of their seizures. However, when a local hospital refused to do genetic testing, the family switched to Cincinnati Children's Hospital, where a genetic test confirmed an *SCN1A* genetic mutation; both boys had Dravet syndrome, a severe and progressive form of epilepsy. In November 2018, Grady Lee passed away from complications caused by the disease.

Like many other families with a loved one suffering from the rare disease, they hope for a cure, but until then, they are focusing on treating Hudson's symptoms to give him the best quality of life possible. Stoke Therapeutics Inc. has shared recent encouraging trial results for their drug aimed at treating a genetic cause of Dravet's syndrome, providing additional hope.

Dravet Syndrome: Frequent, Severe, and Progressive Seizures

Dravet syndrome, also known as Severe Myoclonic Epilepsy of Infancy (SMEI), is a severe and progressive form of epilepsy estimated to affect one out of 16,000 babies. The rare genetic disease — which is not concentrated in any specific geographic area or ethnic group — first appears in infancy and is characterized by frequent, prolonged, and refractory seizures.

Comorbidities of the devastating disease typically appear around age two or three and can significantly impact the patient and caregiver's quality of life. These symptoms often include intellectual disabilities, developmental delays, movement and balance problems, growth and nutrition defects, sleep abnormalities, chronic infections, disruptions of the autonomic nervous system, language and speech disturbances, and mood disorders.

The long-term prognosis is poor, as morbidities for individuals with the disease typically progress throughout their lifetime. Additionally, mortality rates are higher for those with Dravet syndrome compared to the general epilepsy population, with a 15-20% mortality rate due to Sudden Unexpected Death in Epilepsy (SUDEP).

Genetic Mutation: The Underlying Cause of Dravet Syndrome

Approximately 80% of those diagnosed with Dravet syndrome have an *SCN1A* gene mutation, and 90% of these mutations are de novo, meaning the variant was not inherited from the parents but occurred for the first time in the child with epilepsy. Haploinsufficiency, where one copy of the gene functions normally while the other is dysfunctional, is common in Dravet's. When this occurs, the mutated gene does not produce its share of the protein; therefore, the body does not function normally.

The *SCN1A* gene encodes for the voltage-gated sodium channel (VGSC) isoform NaV1.1, which controls the flow of sodium ions across the membrane and generates electrical signals in neurons and muscle tissue. In Dravet syndrome, the variants are typically a loss-of-function mutation that results in a non-functional sodium channel in cells called parvalbumin-positive (PV) inhibitory interneurons. When functioning correctly, these interneurons suppress brain cells from generating electrical activity. However, for those with Dravet syndrome, the mutation impairs the cells' ability to regulate electrical activity effectively, predisposing the individual to seizures.

Currently, available treatment options are limited but include medications to control seizures, vagus nerve stimulation, and adopting a ketogenic diet. Clinical studies have also found that VGSC inhibitors, which are often used to treat epilepsy, can exacerbate seizures in patients with Dravet syndrome. None of these treatments directly address the underlying cause of the disease, but biotechnology company Stoke Therapeutics Inc. aims to change this with their novel gene therapy approach.

STK-001: An Approach Targeting the Underlying Cause of the Disease

STK-001, Stoke Therapeutics Inc.'s investigational new medicine, has the potential to be the first disease-modifying therapy to address a genetic cause of Dravet syndrome. The company's

proprietary approach, Targeted Augmentation of Nuclear Gene Output (TANGO), aims to restore missing proteins by increasing protein output from healthy genes, compensating for the gene's non-functioning copy.

Sometimes, the DNA code of the *SCN1A* mRNA includes a section known as a poison exon within the RNA transcript, which orders the cell to trash the strand of RNA instead of using it to produce the Nav1.1 protein. Using the TANGO platform, Stoke researchers created an antisense oligonucleotide (ASO) that binds to and splices pre-mRNA to promote a process called nonsense-mediated mRNA decay (NMD) exon exclusion, which blocks the inclusion of the poison exon. When TANGO-ASOs trigger this process, it reduces the amount of mRNA that contains non-productive instructions and increases the amount of the productive message responsible for making the sodium channel NaV1.1 proteins.

Additionally, Stoke's approach has the advantage that only the cells naturally expressing *SCN1A* should be affected by the therapy, potentially reducing off-target effects.

Encouraging Data for Dravet Patients

On March 25, 2024, Stoke Therapeutics announced positive new data from Phase 1/2a End of Study Data and Open Label Extension Studies using STK-001 to treat Dravet's syndrome. The drug was found to reduce the frequency of seizures by 43 to 85 percent in 34 patients participating in four early-stage studies. The results differed depending on whether patients received one, two, or three initial 70-mg doses. According to the press release, the patients, ranging in age from two to 18, were highly refractory to treatment, and 80% were already taking at least three of the best available anti-seizure drugs.

The data showed clinically meaningful effects, including substantial and durable reductions in convulsive seizure frequency and improvements in multiple measures of cognition and behavior that reinforce STK-001's potential for disease modification. The reductions in seizures were maintained throughout the treatment.

In the Phase 1/2a study, a combined analysis of 19 clinically evaluable patients treated with one, two, or three doses of 70mg showed substantial reductions in convulsive seizure frequency compared to baseline at three months and six months after the last dose, meeting one of several secondary endpoints in each study. Eligible patients who completed the Phase 1/2a studies then continued STK-001 treatment in one of the two open-label extension studies.

Overall, STK-001 was well-tolerated among patients in the studies. However, some key safety findings include 30% of patients in the Phase 1/2a studies experiencing a treatment-emergent adverse event (TEAE) related to the study drug. The most common TEAE were CSF protein elevations and vomiting. A serious adverse event occurred in 22% of patients in Phase 1/2a, but the events were determined to be unrelated to the drug, except for one patient who experienced Suspected Unexpected Serious Adverse Reactions (SUSARs). In the open-label extension studies, CSF protein elevation was more frequent, with 74% of patients having at least one CSF protein value of >50 mg/dL. No clinical manifestations were observed in these patients.

The company also announced U.S. Food and Drug Administration (FDA) clearance for patients to receive three doses of 70mg followed by continued dosing at 45mg and will meet with regulatory agencies to discuss a regulatory study for these doses.

These improvements come not even a year after Stoke Therapeutics released midstage clinical trial data that revealed a high rate of adverse events and lower than expected improvement in their convulsive seizure frequency. The July 2023 results stated that 14 patients receiving the 45 mg dose had a mean reduction in convulsive seizure frequency of 19% at three months, which jumped to 45% for eight patients at six months. The efficacy was lower than expected after interim results the year prior had found six patients receiving a 45mg dose had a 55% median drop in seizures. The data also showed that one-third of patients experienced an adverse event. However, the most recent results show that multiple doses of the higher 70mg dose provide greater efficacy.

Competition: transfer RNA, CRISPR, and more

Stoke Therapeutics Inc. may be the first drug that addresses a genetic cause of Dravet syndrome to reach clinical trials, but it's far from the only company studying genetic solutions to the disease. Currently, several disease-modifying therapeutic approaches are in different stages of development for Dravet syndrome, and a few are summarized below.

Encoded Therapeutics is working on a potential one-time treatment delivered directly to the brain to increase the expression of *SCN1A*. The drug, known as ETX101, will deliver an engineered transcription factor to cells, and because this is much smaller than the *SCN1A* gene, ETX101 can fit within the commonly used adeno-associated virus (AAV) vector for delivery to cells. Once delivered to the brain, the engineered transcription factor will be expressed in the main type of neurons that use the *SCN1A* gene, known as inhibitory interneurons, and hopefully, restore the function that allows them to reduce or eliminate seizures and other comorbidities of Dravet syndrome. Preclinical work has shown the approach to increase *SCN1A* expression, decrease seizures, and improve survival in a mouse model of Dravet syndrome. The drug has also been well tolerated in non-human primates. Encoded Therapeutics recently received clearance to begin Phase 1/2 clinical trials in the US and Australia. In the US, they are now enrolling patients with SCN1A+ Dravet syndrome who are 6 months to <3 years of age, and those in Australia who are 3 to <7 years old.

CRISPR technology is also being investigated as a potential treatment for Dravet's, but instead of its typical cutting method, it's being used to connect molecules to increase gene expression via a deactivated version of Cas9 called dCas9. The approach is also known as "CRISPR activation" or "CRISPRa," and researchers are looking at how it can increase *SCN1A* expression by targeting dCas9 to specific regulatory regions for *SCN1A*. Cell lines and mouse models of Dravet syndrome have shown the approach can work and improve neuronal communication and seizure activity in mice. However, the work is still in preclinical development, and challenges to its delivery methods and the efficiency of increasing gene expression must be solved before making the jump to patients.

Tevard Biosciences, which an MIT molecular biologist founded alongside two parents of children with Dravet's, is working on two therapies that use transfer RNA (tRNA) to correct the *SCN1A* haploinsufficiency in Dravet syndrome. The first therapy targets nonsense mutations, which causes the cell to prematurely stop making the Nav1.1 protein, thus creating a shortened version that either gets broken down by the cell or doesn't work efficiently. The approach uses tRNA to overcome the nonsense mutation by reading through the premature stop signal and allowing Nav1.1 to be correctly made into a full-length protein. Tevard's other therapy uses tRNA to help stabilize the *SCN1A* mRNA so it can be used to create more copies of the Nav1.1 protein. Like ETX101, these therapies would be delivered to the brain via an AAV vector as a one-time therapy. However, the technology is still in its preclinical phase, with the company working on animal models of Dravet syndrome.

Other areas of therapy being investigated include how altering other genes in the same pathway as *SCN1A* could compensate for the reduced *SCN1A* expression in Dravet's. One research group has tried sending in another copy of a gene (NaV1B) that interacts with Nav1.1., which had mixed results based on sex in mouse models of Dravet syndrome and a modest impact on seizures. Decreasing expression of a separate sodium channel gene, *SCN8A*, has also been studied and was found to eliminate behavioral motor seizures for five months post-treatment and reduce mortality in a mouse model of Dravet syndrome.

Additionally, other companies are enrolling patients in clinical trials to investigate drugs that are not oligo approaches to control seizure frequency. Harmony Biosciences phase 2 ARGUS Study is testing EPX-100 (Clemizole Hydrochloride) as an adjunctive therapy for adults and children 2 years and older with Dravet syndrome who suffer from uncontrolled seizures. The Jazz Piccolo Study is investigating the safety and effectiveness of cannabidiol in children two years or younger whose seizures are not adequately controlled. Children in this trial may have been diagnosed with Dravet Syndrome (DS), Tuberous Sclerosis Complex (TSC), or Lennox-Gastaut Syndrome (LGS).

The Future of Dravet Syndrome Treatment

For newly diagnosed Dravet families, the parents of Hudson Blake and Grady Lee encourage them not to lose hope. Since the twin's diagnosis, new medications have been FDA-approved, and more therapies are in the pipeline. Regardless of the approach, significant research into treating Dravet syndrome is an encouraging sign for both those with the disease and their caregivers. As companies like Stoke and Encoded move onto their next phase of clinical studies, the Dravet community hopes to see encouraging results continue towards providing a treatment that modifies the course of the disease.