

## Gene Therapy for Dravet Syndrome - when and how?

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Recent reports of exciting progress in gene therapy for the early onset neurological disorder Spinal Motor Atrophy (SMA) has raised the question in all of our minds - when will Dravet Syndrome patients benefit from this breakthrough? The potential for gene therapy is different for every genetic disorder, and there are many specific factors to consider. It may be helpful to look at some recent successes and compare them with what would be needed for gene therapy of Dravet Syndrome. In each of the recent success stories differs in an important way from Dravet.

Spinal motor atrophy is a deficiency disorder, like Dravet Syndrome, that is caused by mutation of the gene SMN1. In this case, there is a closely related gene, SMN2, that is not normally active because a sequence in intron 7 of the gene prevents the splicing of exon 7 into the messenger RNA. Dr. Adrian Krainer at Cold Spring Harbor Laboratory discovered that a small DNA fragment (an ASO) that binds the intron 7 sequence can activate the splicing of exon 7. In this special situation, administration of the ASO via injection into the cerebral spinal fluid results in activation of SMN2 and clinical improvement, based on early results from a Phase 3 clinical trial. Repeated injection of the ASO is required to maintain expression of SMN2. Unfortunately, in the case of Dravet Syndrome there is no extra copy of the *SCN1A* gene that could be activated in this way.

Treatment with short DNA fragments (ASOs) also shows promise for the triplet expansion disorders such as Huntington's Disease. The mutant gene contains a long stretch of nucleotide repeats that is not present in the normal gene. Targeting with ASOs prevents expression of the mutant allele, resulting in clinical improvement in mouse models. Phase 1 trials for Huntington patients are in progress. This approach is being developed for other triplet expansion diseases such as Spinal Cerebellar Ataxia. Turning off a dominant mutant gene with ASOs is sometimes referred to as Gene Suppression. Gene Suppression is not applicable to Dravet Syndrome, because it is a deficiency disorder.

Another type of gene therapy for deficiency disorders like Dravet Syndrome is gene replacement. The mRNA encoding the deficient gene is cloned into an RNA virus that can be injected into the cerebrospinal fluid and then enters neurons in the brain. This approach is under development for several lysosomal storage diseases and other disorders. The currently available viruses can accommodate a messenger RNA of length up to 4,500 nucleotides. However, the *SCN1A* mRNA is 6,000 nucleotides long, and the entire protein seems to be required for channel activity. Thus gene replacement with viral vectors is not yet feasible.

The Duchene Muscular Dystrophy gene encodes a very large protein, but in this case a functional protein is still produced after deletion a large portion of the mRNA. Two types of

treatment, ASOs to change splicing and viral vectors to deliver the short protein, show promise as treatment for Duchene Muscular Dystrophy.

As you can see, each genetic disorder has unique features, and therapy for each disease must be tailored to each specific gene. In the case of Dravet Syndrome, there is deficiency due to mutation of one copy of the *SCN1A* gene, and patients retain one good copy of the gene. It is very attractive to consider increasing the expression level of the good copy of *SCN1A*, but no one knows how to do that yet. Stabilization of the messenger RNA or protein are being considered. Unfortunately, the *SCN1A* messenger RNA is too large for current viral vectors. We do not know of any target to 'knock-down' with an ASO, as for Huntington's Disease, or any target to activate with an ASO, as for Spinal Motor Atrophy. So we are challenged to come up with something new, through basic research, that will enable us to compensate for *SCN1A* deficiency. However, the delivery methods for gene therapy are currently being improved in many laboratories, and after a good target is identified for increasing *SCN1A* expression, we can expect to see rapid progression into animal models and to the clinic.