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Epilepsy Therapy Goes Viral

Epilepsy Gene Therapy Using an Engineered Potassium Channel

Snowball A, Chabrol E, Wykes RC, Shekh-Ahmad T, Cornford JH, Lieb A, Hughes MP, Massaro G, Rahim AA, Hashemi KS, Kullmann DM, Walker MC, Schorge S. *J Neurosci*. 2019;39(16):3159-3169. doi:10.1523/JNEUROSCI.1143-18.2019

Refractory focal epilepsy is a devastating disease for which there is frequently no effective treatment. Gene therapy represents a promising alternative, but treating epilepsy in this way involves irreversible changes to brain tissue, so vector design must be carefully optimized to guarantee safety without compromising efficacy. We set out to develop an epilepsy gene therapy vector optimized for clinical translation. The gene encoding the voltage-gated potassium channel Kv1.1, KCNA1, was codon optimized for human expression and mutated to accelerate the recovery of the channels from inactivation. For improved safety, this engineered potassium channel (*EKC*) gene was packaged into a nonintegrating lentiviral vector under the control of a cell type-specific CAMK2A promoter. In a blinded, randomized, placebo-controlled preclinical trial, the EKC lentivector robustly reduced seizure frequency in a male rat model of focal neocortical epilepsy characterized by discrete spontaneous seizures. When packaged into an adeno-associated viral vector (AAV2/9), the *EKC* gene was also effective at suppressing seizures in a male rat model of temporal lobe epilepsy. This demonstration of efficacy in a clinically relevant setting, combined with the improved safety conferred by cell type–specific expression and integration-deficient delivery, identifies *EKC* gene therapy as being ready for clinical translation in the treatment of refractory focal epilepsy.

Keywords
epilepsy, virus, gene therapy, KCNA1, neocortical focal epilepsy

Commentary

Gene therapy has been envisioned since the 1970s but has faced a number of difficult obstacles, both in the laboratory and the clinic. Following early success of a clinical trial for adenosine deaminase - severe combined immunodeficiency (ADA-SCID) in 1990, subsequent clinical failures quickly led to dismissal of gene therapy as nothing more than an experimental technique. However, over the last 15 years, there have been dramatic improvements in human genetics, genome editing strategies, methods for gene delivery, and disease modeling, all of which has made this innovative therapeutic strategy move at an increasingly rapid pace toward every day clinical practice.[1] This has led to a renewed interest in the promise of gene therapy for a wide range of human diseases, highlighted by a recent Food and Drug Administration approval for the treatment of spinal muscular atrophy.[2] However, despite many convincing advances in the field, antiepileptic gene therapy remains at a preclinical proof-of-principle stage. There are a number of important challenges that must be overcome in order to move this exciting technology to the clinic for epilepsy, such as choice of gene or pathway to target, viral packaging, off-target effects, successful delivery into the human brain, safety, and even the inherent heterogeneous etiology of epilepsy itself. With potentially more than 100 genes reported to cause epilepsy,[3] many of which are expressed throughout the brain and/or body, it is difficult to envision applying the traditional concept of gene therapy (ie, to fix a defective gene or pathway) for each individual monogenetic disorder. In contrast, approaches that target more downstream pathways to manipulate the expression of genes that control neuronal or circuit excitability in affected brain areas may have broader application.[4]

Snowball and colleagues built upon their prior work[5,6] developing a viral vector–mediated gene therapy to alter neuronal and circuit excitability in focal neocortical epilepsy. This approach involves overexpression of the human *KCNA1* gene, which encodes the voltage-gated potassium channel Kv1.1, in epileptogenic foci. Here, the authors engineered and optimized the viral construct used in earlier studies with the goal of generating an effective gene therapy that might be ready for clinical translation. To do this, they first replicated and extended

their prior work by demonstrating a dramatic suppression of spontaneous seizures following the delivery of a CMV-driven *KCNA1* lentivirus directly into the seizure focus in visual cortex of a tetanus toxin model. This construct was then modified in 3 main ways: (1) the non-cell-type-specific CMV promotor was exchanged for a *CAMK2A* promotor to drive Kv1.1 expression in excitatory projection neurons, (2) the Kv1.1 gene was modified to reduce its inactivation, and (3) the resulting plasmid was packaged into a nonintegrating lentiviral vector to reduce the potential risk of mutagenesis. This new, refined construct had even more powerful therapeutic effects on seizures in the tetanus toxin model of focal epilepsy, presumably due to increased specificity for targeting excitatory neurons, and it was also effective in a kainic acid model of temporal lobe epilepsy, when packaged into an AAV vector and injected bilaterally into hippocampus.

Neocortical epilepsy is often drug-resistant, and surgery to remove the epileptogenic zone is not always feasible or effective. As such, development of a spatially restricted, cell-type-specific gene therapy that selectively modifies the activity of neurons at the seizure focus could be an important advance. If successful, this strategy might also spare unaffected brain regions or minimize the types of side effects seen in current pharmacological approaches. Although the results reported by Snowball and colleagues are promising, additional hurdles remain before eventual translation to the clinic. For example, the authors only evaluated the effect of this gene therapy on seizures, and it is not yet known how overexpression of Kv1.1 in *CAMK2A* neurons might alter visual cortex function. In thinking about moving from rodent to human, large animal studies may be necessary for determining how to precisely deliver the vector to epileptic foci of a gyrated neocortex.

Ultimately, for clinical trials to succeed, one must decide who will be an appropriate candidate for therapy. A patient with drug-resistant epilepsy and a well-defined focal lesion in eloquent cortex has been considered to be an ideal candidate. The most prevalent pathologic substrate of epilepsy surgery is focal cortical dysplasia, which has been identified in both magnetic resonance imaging positive and negative cases.[7] However, if a gene therapy is effective and safe, and can be broadly applied to many forms of the disease as indicated in the current study, it may be advantageous to develop this technology for a wider range of patients regardless of whether or not a focal epileptogenic zone is present. It is possible that such a therapy could be useful in acquired epilepsy, such as following a traumatic brain injury or stroke, as well as in genetic epilepsies. As such, this study by Snowball and colleagues provides an important step closer to achieving successful gene therapy for epilepsy.

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