

OPINION

Gene therapy in epilepsy—is it time for clinical trials?

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Abstract | Epilepsy represents a major burden to society, not least because approximately 25% of patients do not respond satisfactorily to antiepileptic medication, and only a minority with pharmaco-resistant epilepsy are eligible for potentially curative surgery. Several studies have explored gene therapy as a treatment strategy. The translation of scientific breakthroughs into the clinic faces several challenges, including the validation of experimental models of human pharmaco-resistant epilepsy, establishment of sensitive and specific measures of therapeutic efficacy, and evaluation of the long-term safety of gene therapy. On the basis of successful reports of gene therapy in experimental models of epilepsy, a roadmap toward clinical trials is proposed.

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Introduction

Epilepsy represents an enormous health and socioeconomic burden: it is common and has devastating consequences for people who do not respond satisfactorily to medication. These patients (approximately 0.2% of the population in developed countries) have very few treatment options.^{1–3} Surgery to remove the epileptogenic zone is only appropriate in a minority of people with focal-onset seizures, and is often contraindicated by proximity of the lesion to eloquent cortex.³ Alternative treatments such as ketogenic diets or vagus nerve stimulation have limited efficacy, and deep brain stimulation,⁴ targeted drug delivery,⁵ focal cooling,⁶ cell transplantation⁷ and gene therapy are still at the experimental stage. Of these approaches, we suggest that gene therapy holds the most promise on the basis of the molecular tools available and the ability to design strategies to achieve region-specific and cell-specific modification of neuronal and circuit excitability. The viral vectors that are used to deliver transgenes are increasingly reliable in terms of expressing the transgene, and data on long-term safety are accumulating from other neurological diseases.⁸ Several preclinical studies of viral gene therapy for epilepsy have been

conducted over the past decade, with promising results.^{8–21} The potential to translate gene therapy research to human pharmaco-resistant epilepsy is not straightforward, however. In this Perspectives article, we outline a roadmap toward clinical trials (Figure 1), which takes into account the development of experimental models of epilepsy, viral vectors and new molecular tools, and the clinical scenarios in which gene therapy could be informatively and ethically tested.

Epilepsy Preventing epilepsy

There are various causes of epilepsy, including stroke, traumatic brain injury and encephalitis. In principle, preventing the development of epilepsy (epileptogenesis) would represent an important breakthrough. Indeed, several preclinical studies have reported success in attenuating or preventing epileptogenesis.^{9–21} However, epidemiological studies indicate that the risk of developing epilepsy after any major brain insult is rarely greater than 10%,^{22–24} and the risk of developing pharmaco-resistant epilepsy is lower still. Until it is possible to accurately identify those individuals who will develop epilepsy in the long term, the translation of successful antiepileptogenic therapies from animal models to humans will be hindered ethically and practically by

the need to treat more people than necessary. This problem may be addressed in the future by identifying biomarkers that predict the development of epilepsy after such insults. Until biomarkers are identified and validated, we suggest that it would be more practical to assess the safety and efficacy of gene therapy in patients with established epilepsy.

Preclinical models

Historically, antiepileptic drugs have been tested in a small number of animal models. Some of these models, such as those with acute electrically or chemically induced seizures, are of limited translational value,²⁵ as they do not reflect the clinical situation in which seizures occur spontaneously. Importantly, they also fail to simulate pharmaco-resistant epilepsy.

A useful preclinical model of epilepsy in which to evaluate gene therapy with a view to clinical translation, therefore, is one with spontaneous seizures that occur at a sufficiently stable frequency to enable detection of an effect of treatment. Other desirable features include seizures that respond poorly to currently available drugs, and a restricted (and identifiable) seizure focus that can be targeted for gene therapy.

Rodent models of chronic mesial temporal lobe epilepsy (MTLE) following chemoconvulsant-induced or electrically induced status epilepticus approximate this description.²⁶ Even though surgery to resect the epileptogenic zone is an effective treatment in over three-quarters of patients with refractory MTLE,²⁷ only 50% remain seizure-free for 10 years,²⁸ arguing that new therapies are needed. Moreover, although temporal lobectomy is safe (<1% mortality), a therapy without the morbidity associated with temporal lobectomy (in particular, detrimental effects on memory) would potentially be advantageous.²⁹ A potential limitation of rodent models of MTLE is that the hippocampal formation is comparatively large relative to the rest of the brain, and that the seizure focus is often bilateral, necessitating treatment to both temporal lobes.

Another potentially informative rodent model, chronic thalamocortical epilepsy, has been reported.^{30,31} This condition develops,

Competing interests

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after a delay, in approximately 50% of rats in which neocortical stroke has been induced by photothrombotic occlusion of a large-vessel. Although pharmacoresistance has not been evaluated systematically in this model, a positive response to gene therapy has been shown using targeted expression and photactivation of the inhibitory optogenetic actuator halorhodopsin in the thalamus.³²

A third experimental model that has attracted attention is the development of spontaneous seizures after tetanus toxin injection in various cortical and sub-cortical brain regions.^{33,34} This model of epilepsy is long-lasting, is often resistant to currently available antiepileptic drug therapy,³⁵ and potentially enables evaluation of treatment of eloquent regions of the cortex.^{36–38} The frequency of seizures in this model is stable enough to measure both reversal of established seizures and prevention of epileptogenesis after experimental gene therapy.¹⁴ The difficulties encountered with this model include variable potency of commercially available tetanus toxin samples.

Gene therapy Manipulating endogenous genes

The choice of endogenous genes to target is informed by basic research in biophysics and synaptic physiology. Increased understanding of the functional effects of mutations that cause epilepsy³⁹ has provided new strategies to prevent seizures by reversing these effects. In this section, we highlight some of the approaches that have been reported.

Vectors driving expression of the neuropeptides galanin^{12,13} and neuropeptide Y (NPY), either in isolation or together with inhibitory Y receptor type 2,^{9,10,16,40} have shown promise in disrupting epileptogenesis by increasing the seizure threshold or decreasing the number of seizures. NPY was also effective in a model of established epilepsy.¹⁰ These neuropeptides are thought to inhibit the release of glutamate from presynaptic terminals, in principle limiting the spread of seizures or even preventing the genesis of seizures. Neuropeptides are also thought to act via volume transmission, affecting targets remote from their site of release, which suggests they may even reach neurons that are not postsynaptic to transduced neurons. Purinergic inhibitory transmission might also be effective in the treatment of epilepsy; however, we are only aware of experimental therapies based

on cell transplantation or polymer-based gene delivery that have used this approach with some success, which are beyond the scope of this Perspectives article.⁴¹ Increased expression of the $\alpha 1$ subunit of the γ -aminobutyric acid (GABA_A) receptor has also been reported to delay the occurrence of seizures and to decrease the number of seizures in the first 2 weeks after status epilepticus.¹⁹ The efficacy of this approach has not yet been reported in a model of established epilepsy.

We have shown that decreasing the excitability of pyramidal neurons in an epileptic focus by overexpression of a human potassium channel protein is effective in experimental models both of epileptogenesis and of established epilepsy.¹⁴ K_v1.1, the voltage-gated potassium channel that was used in this study, is only one of a large family of voltage-gated channels, and whether or not a similar effect could be achieved by overexpressing other proteins that contribute to hyperpolarization of neurons remains to be determined.

RNA interference (also called post-transcriptional gene silencing) to target individual excitatory channels has also been proposed as a therapeutic strategy, although relatively little is known about the optimal delivery route, duration of effect and risk of off-target effects compared with viral gene therapy.^{42,43}

Targeting cohorts of genes

One step away from the targeted manipulation of single genes is the reversal of widespread changes in gene expression that occur during epileptogenesis. Several studies propose different means to achieve this goal. First, inhibiting the actions of neuron-restrictive silencing transcription factor (NRSF) blocks some of the changes in neuronal intrinsic excitability that accompany epileptogenesis, reduces the frequency of seizures, and restores normal EEG recordings.²⁰ A reduction in the number of seizures after oligonucleotide-mediated knockdown of NRSF suggests that manipulating this gene with virally delivered short hairpin RNA might be beneficial for restoring network excitability, although any strategy that relies on altering the expression of transcription factors calls for an exhaustive search for off-target effects, owing to the potentially large number of genes downstream that could be modified. A conceptually similar but mechanistically different approach is to increase or decrease the expression of microRNAs

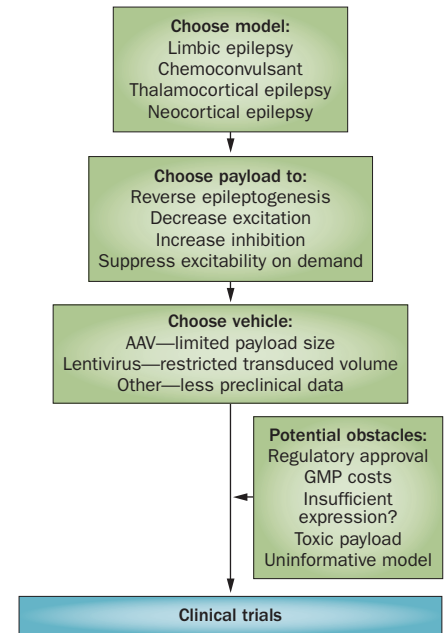


Figure 1 | A patient-centred approach to gene therapy for epilepsy. The first step is to choose an animal model that best matches the highest clinical need, followed by the therapeutic approach to relieve seizures. Once the target and treatment are identified, this information can be used to determine the best vector for delivery. During this process, anticipation of potential obstacles might save inadvertent returns to preclinical testing (for example, due to trivial changes in vector backbones or intellectual property issues). First-in-human trials of gene therapy are only possible with a safe, effective vector, targeting a condition that makes invasive treatment clinically justifiable.

(miRNAs) that regulate cohorts of genes. Targeting of miRNA-134 suppresses the development of chronic seizures and has a neuroprotective effect.²¹

Growth factors contribute to a host of cellular changes (neuronal and glial) during epileptogenesis and these provide another avenue for treatment. A combined fibroblast growth factor 2 (FGF-2) and brain-derived neurotrophic factor (BDNF) expression vector administered to rats shortly after status epilepticus substantially reduced the expression of several markers of epileptogenesis, even during the early latent period (3 days after status epilepticus).¹⁷ However, this treatment did not decrease the frequency of spontaneous seizures if administered to rats after epilepsy was established (3 weeks),¹¹ so the potential for translation to the clinical treatment of established epilepsy is limited.

Research on transcription factors that are consistently upregulated in human

epilepsy and in chronic epilepsy models has prompted experimental manipulation of the inflammatory regulator Nrf2. In one study, treatment was effective 3 weeks after status epilepticus,⁴⁴ suggesting that this approach may have efficacy in established epilepsy. Furthermore, these approaches hold the appeal of theoretically restoring neurons to their pre-epileptic state, by reversing the widespread changes in gene expression and regulation that disrupt the balance between excitation and inhibition. However, approaches that alter the expression of many genes also carry a theoretical risk of off-target effects on other—as yet uninvestigated—signalling cascades, thereby placing an additional burden on preclinical testing.

Exogenous or engineered molecules

A further development in gene therapy is to introduce novel engineered or exogenous proteins into the brain to manipulate neuronal excitability. This field is fast-moving, and is currently dominated by the use of light-sensitive proteins in optogenetic approaches to treat epilepsy. Several research groups have used the inhibitory chloride transporter halorhodopsin to suppress neuronal excitability and interrupt seizures.^{14,32,45,46} In one study, promising results were achieved with an optogenetic approach that involved targeting of the excitatory actuator channelrhodopsin-2 to GABAergic interneurons in order to increase inhibitory signalling.⁴⁷ The ability to use optogenetics to turn light-gated ion channels on or off in response to detection of a seizure is especially attractive because it potentially enables targeted neuronal circuits to operate normally at other times.

These approaches increase the burden of preclinical safety testing, in particular to assess adverse immune responses. Although these approaches are far from the clinic, a theoretical advantage is that they might be used to test both anti-epileptogenic and antiseizure strategies: the proteins could be expressed before the insult, and only activated at desired stages of epileptogenesis.

Choice of vector

A growing number of genetically modified viruses are being developed as vectors that can be used for heterologous gene expression in neurons. Most attention has been given to lentiviruses and adeno-associated viruses (AAVs). Other viral vectors are able to infect postmitotic cells such as neurons,

but may be neurotoxic or trigger immune responses; examples include herpes simplex virus, adenovirus, rabies virus and Semliki Forest virus. Both AAVs and lentiviruses seem to be well-tolerated, and lentiviruses in particular do not elicit strong immune responses in experimental animals. Many other neurotropic viruses, including polio, mumps, and other herpes family viruses, are awaiting characterization,⁴⁸ and will require additional preclinical testing to demonstrate safety prior to administration to patients. The use of established viral backbones, or vectors already approved for use in other human diseases, might be an effective way of speeding up the translation of gene therapy to clinical trials. Collaboration between research groups with insights into the pathophysiology of epilepsy and groups with expertise in virology might be required to avoid triggering further preclinical safety studies due to clinically unnecessary modifications of viral backbones.

AAV serotypes with different tropisms have been recombined to confer an ability to cross the blood–brain barrier, raising the possibility of systemic delivery of a virus to target neurons without the need for surgery.⁴⁹ However, there are major hurdles to using AAVs, including their small transgene capacity (~2 kb of DNA), which prevents the use of long expression constructs or regulatory sequences. Moreover, many individuals have high natural immunity to certain viral serotypes, and acquired immunity could potentially complicate repeated treatment.

Lentiviral expression constructs can carry a much larger transgene (~6 kb of DNA) than AAV vectors, which opens up the possibility of using specific promoters, including promoters that can be induced in response to oral drugs. However, lentiviruses tend to transduce neurons in a small brain region⁵⁰ and as yet cannot be delivered systemically, suggesting that they need to be injected into the epileptogenic zone. This approach might be advantageous when the epileptic zone can be defined with precision, but it makes lentiviruses unlikely tools for the treatment of epilepsies with a genetic cause or in which a single focus cannot be found. Concerns about chromosomal mutagenesis owing to insertion of viral genes have not prevented a clinical trial of gene therapy in Parkinson disease.⁵¹ Furthermore, nonintegrating expression constructs have been developed that, in principle, minimize the risk of oncogene activation.⁵² Although nonintegrating

lentiviruses lead to decreased gene expression in dividing cells this should not pose a problem in postmitotic cells such as neurons.

The main advantage of herpes simplex viruses is that they can deliver large transgenes (>20 kb of DNA).⁸ A herpes simplex viral vector expressing FGF-2 and BDNF has been used in experimental models of epilepsy.^{11,17} These viruses have also been investigated extensively for use in cancer therapy to trigger oncolysis.⁵³ Before translation into gene therapy for epilepsy, additional preclinical development may be necessary to ensure that these vectors have no neurotoxic or immunogenic effects. Finally, several nonviral mechanisms exist for manipulating gene expression, but are beyond the scope of this article.

Measuring efficacy

Once a model of epilepsy has been chosen, and a gene therapy vector constructed, the efficacy of this approach must be established, preferably using robust and clinically relevant outcomes. From a clinical perspective, the primary end point is a reduction in—and ideally the complete cessation of—clinical seizures. Clinical seizures not only consist of an abnormal discharge from neurons that is detectable on EEG, but also include accompanying symptoms and/or signs such as motor convulsions or altered consciousness. A secondary end point is neuroprotection; that is, prevention of neurodegeneration that might accompany epileptogenesis. Other end points include a reduction in the frequency and/or severity of interictal epileptiform discharges and subclinical seizures that may have functional consequences, including disrupted cognitive processing.^{54,55} Finally, comorbidities such as depression, decline in cognitive function and increased mortality are important concerns for patients and, consequently, should also be borne in mind.

An ideal gene therapy strategy should stop seizures, and most studies have reported EEG recordings with video confirmation of behavioural correlates. However, it is important to remember that nonmotor correlates of seizures in preclinical studies may be missed by video monitoring. Video recording is most helpful to identify seizures that generalize, as focal seizures that affect a single limb may be difficult to detect in rodents, and absence seizures might be accompanied only by behavioural arrest. Seizures that manifest with only sensory or experiential symptoms may have no obvious

behavioural signs in animal models, so reliance on EEG is inevitable.

The EEG power over long recording periods can be analysed, especially in high-frequency bands, or the 'coastline' (that is, the cumulative absolute difference in voltage between successive data points) of the EEG can be measured. A more specific measure of the severity of epilepsy is to count the frequency, power and duration of discrete epileptiform events on EEG, with attention to circadian rhythms and nonepileptic artefacts. Finally, histological assessments in experimental models can be made to determine whether or not a treatment also prevents neuronal death, particularly if the model exhibits extensive neuronal death in the absence of treatment. Other behavioural tests such as measures of learning, anxiety and depression can also be included to determine the extent of comorbid effects of epilepsy and seizures.

Clinical translation

Gene therapy approaches that modify endogenous genes, target small brain regions and do not introduce the expression of foreign proteins are generally considered as safe. However, concerns remain that gene therapy strategies that modify the expression of a single gene could be compensated for by the altered expression of other endogenous genes, leading to widespread changes in synaptic, neuronal or circuit excitability.

The introduction of gene therapy vectors into the brain is effectively irreversible; therefore, stringent toxicity and biodistribution studies are required.^{56,57} These studies might be facilitated by the development of online toxicology databases.⁵⁸ Clinical studies of any therapy typically require certified standards of purity, so it is often necessary to outsource the later stages pre-clinical studies to contract research organizations. Indeed, researchers and clinicians are becoming increasingly aware of the need to streamline the development of gene therapy tools to the clinic.⁵⁹

Although various steps can be taken to regulate the expression of transgenes, the vector itself, once injected into the brain, still has the potential to alter the genetic complement of infected neurons permanently. In gene therapy for focal epilepsy, however, lentiviral and some AAV vectors only infect neurons in a small brain region.⁶⁰ In principle, surgical excision could be used to remove transduced neurons completely in the event that the treatment

was unsuccessful or was accompanied by adverse effects. This safety net could prompt the design of a first-in-human clinical trial in which gene therapy is offered, not initially to patients with inoperable epileptogenic zones, but to patients who are deemed suitable for conventional epilepsy surgery. Provided that the vector is targeted correctly to the epileptogenic zone and the seizures remit after gene therapy, ablative surgery could be avoided. A patient could still proceed to removal of the epileptic region that had been transduced with the vector if therapy failed, and this tissue could then be studied *ex vivo* to assess the extent and specificity of neuronal transduction, and even its consequences for neuronal excitability. *Ex vivo* studies such as this could help researchers to determine the reasons for therapeutic failure, such as insufficient transduction or lack of cell-type specificity. A clinical trial of this kind would be the first step in moving toward gene therapy in individuals with seizures arising from eloquent cortex, with the long-term aim of providing therapeutic options to patients with drug-resistant focal epilepsy, for whom few treatment options are available.

Conclusions

To steer the development of gene therapy, we advocate focusing on patient needs. This approach begins with the choice of experimental model, and ends with an appropriate measure of efficacy, including but not limited to a reduction in seizures and epileptiform EEG abnormalities. The current risk-to-benefit ratio of gene therapy argues for the development of treatments for patients who need it most; that is, patients with drug-resistant epilepsy for whom other treatment options are limited.

Gene therapy has already been used in Parkinson disease, and reports of successful treatment in non-neurological disorders are beginning to emerge. For epilepsy, a series of potential gene therapy approaches are available, largely developed from decades of research into what dampens seizures. To move forward, these approaches must be tested in experimental models that best replicate the clinical situation in which invasive gene therapy treatment is warranted. Scientists must move on from using experimental models of induced convulsions and turn their attention to establishing the efficacy of therapeutic strategies to treat spontaneous seizures once epilepsy is established, ideally in more than one animal

model. Overall, their efforts should be directed at treating the types of epilepsy that are the most disruptive and are refractory to known treatments.

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Author contributions

All authors researched the data for the article, provided substantial contributions to discussions of its content, wrote the article and undertook review and/or editing of the manuscript before submission.