







# Epilepsy Benchmarks Area III: Improved Treatment Options for Controlling Seizures and Epilepsy-Related Conditions Without Side Effects

Epilepsy Currents  
2020, Vol. 20(15) 235-305  
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DOI: 10.1177/1535759719895279  
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## Abstract

The goals of Epilepsy Benchmark Area III involve identifying areas that are ripe for progress in terms of controlling seizures and patient symptoms in light of the most recent advances in both basic and clinical research. These goals were developed with an emphasis on potential new therapeutic strategies that will reduce seizure burden and improve quality of life for patients with epilepsy. In particular, we continue to support the proposition that a better understanding of how seizures are initiated, propagated, and terminated in different forms of epilepsy is central to enabling new approaches to treatment, including pharmacological as well as surgical and device-oriented approaches. The stubbornly high rate of treatment-resistant epilepsy—one-third of patients—emphasizes the urgent need for new therapeutic strategies, including pharmacological, procedural, device linked, and genetic. The development of new approaches can be advanced by better animal models of seizure initiation that represent salient features of human epilepsy, as well as humanized models such as induced pluripotent stem cells and organoids. The rapid advances



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in genetic understanding of a subset of epilepsies provide a path to new and direct patient-relevant cellular and animal models, which could catalyze conceptualization of new treatments that may be broadly applicable across multiple forms of epilepsies beyond those arising from variation in a single gene. Remarkable advances in machine learning algorithms and miniaturization of devices and increases in computational power together provide an enhanced opportunity to detect and mitigate seizures in real time via devices that interrupt electrical activity directly or administer effective pharmaceuticals. Each of these potential areas for advance will be discussed in turn.

### Keywords

NINDS benchmarks for epilepsy research, Epilepsy Benchmarks, progress in epilepsy research, seizure mechanisms, refractory epilepsy, genetics, real-time management of seizures, epilepsy therapies

## Introductory Vignette by Amanda Jaksha: Clinical Trials—A Parent’s Perspective

CDKL5 deficiency disorder (CDD) is a rare developmental and epileptic encephalopathy that typically presents with refractory epilepsy, often epileptic spasms without hypsarrhythmia, in the first days or months of life. In 2012, at the age of 6.5 years, my daughter was diagnosed with CDD. By then, she had endured thousands of seizures and failed most available AEDs. She narrowly escaped liver failure from drug rash with eosinophilia and systemic symptoms syndrome upon the introduction of a second-generation AED adjunct therapy. Also seasoned in failed treatments for comorbidities of dysmotility, behavior, and sleep, we become cynical about introducing any compounds.

We recently convened serious discussions about seizure control due to a decrease in her quality of life, with puberty onset increasing daily seizure activity. My daughter was a candidate for 2 clinical trials, one a blinded, placebo-controlled study and the other an open-label investigation. It was a simple choice as there was no time for a placebo. Upon completion of the observation period, she received her first dose around 6 weeks later. There was an immediate increase in seizures, and a few days later, a gradual reduction from baseline activity emerged. Anxiety and vocal stimming behaviors decreased substantially, and her gross motor skills became more fluid and sustained. With these improvements, she enjoys more functional access to community and more independence with the ability to ambulate longer distances. She also appreciates expressing more of her voice as she uses her eyes to talk via an eye-gaze communication (AAC) device. She can tell me to go away or that she feels diabolical with higher efficiency and less frustration. While her epilepsy remains refractory, to our surprise and delight, her quality of life has increased beyond anything imagined with this assumed improvement in other neuronal functions.

—Amanda Jaksha, International Foundation for CDKL5 Research

## Introduction to Area III

The goals of Epilepsy Benchmark Area III involve identifying areas that are ripe for progress in terms of controlling seizures and patient symptoms in light of the most recent advances in

both basic and clinical research. These goals were developed with an emphasis on potential new therapeutic strategies that will reduce seizure burden and improve quality of life for patients with epilepsy. In particular, we continue to support the proposition<sup>1</sup> that a better understanding of how seizures are initiated, propagated, and terminated in different forms of epilepsy is central to enabling new approaches to treatment, including pharmacological as well as surgical and device-oriented approaches. The stubbornly high rate of treatment-resistant epilepsy—one-third of patients<sup>2</sup>—emphasizes the urgent need for new therapeutic strategies, including pharmacological, procedural, device linked, and genetic. The development of new approaches can be advanced by better animal models of seizure initiation that represent salient features of human epilepsy,<sup>3</sup> as well as humanized models such as induced pluripotent stem cells (iPSCs) and organoids.<sup>4</sup> The rapid advances in genetic understanding of a subset of epilepsies<sup>5,6</sup> provide a path to new and direct patient-relevant cellular and animal models, which could catalyze conceptualization of new treatments that may be broadly applicable across multiple forms of epilepsies beyond those arising from variation in a single gene. Remarkable advances in machine learning algorithms and miniaturization of devices and increases in computational power together provide an enhanced opportunity to detect and mitigate seizures in real time<sup>7,8</sup> via devices that interrupt electrical activity directly or administer effective pharmaceuticals. Each of these potential areas for advance will be discussed in turn.

## Seizure Mechanisms

There remains a pressing need to understand the initiation, propagation, and termination of seizures at the network level in different forms of epilepsy in order to devise better treatment strategies. Understanding how neuronal synchrony within a microcircuit reaches a critical threshold, subsequently allowing it to entrain larger populations of neurons, could suggest novel mechanisms that can be engaged to terminate a seizure. Although there are volumes of work on this topic over the decades,<sup>9-11</sup> new advances in stratification of epilepsies through pharmacogenomics<sup>12</sup> and genetic analysis<sup>13</sup> could provide new understanding of mechanisms in models relevant for human disease. Advances in computational models have



reached the point where both interictal and ictal activities can be reliably generated from the same network. The predictions of these models can now be practically verified.<sup>14,15</sup> Additional insights may also follow from a determination of the relative contribution of shared cellular and network mechanisms to different models. Similarly, advances in modeling the process of epileptogenesis suggest interesting new mechanisms, yet highlight the complexity of the problem.<sup>16</sup> These mechanisms could lead to the testing of more effective therapies.

Status epilepticus remains a clinical challenge, with a subset of patients proving refractory to multiple treatments<sup>17</sup> despite the development and approval of new antiseizure medications (ASMs). The persistent seizures associated with this condition focus attention on how little we understand about the processes of seizure initiation, maintenance, and termination. Thus, insight into mechanisms that maintain hypersynchronous firing for prolonged durations in the face of adaptive changes, exhaustion of energy stores, and mounting inflammatory cascades may allow improved treatments that can stop ongoing seizures and status epilepticus. Although a variety of processes are considered relevant to status epilepticus,<sup>18-20</sup> we still lack a clear assessment of the relative contributions of each one. New mechanism-based targets would improve our ability to effectively terminate status epilepticus.

An impressive amount of electrophysiological analysis of mechanisms that can lead to hypersynchronous firing has been performed either *in vivo* in adult animals or *ex vivo* in brain slices from rodents that range in age from adolescence to young adulthood. There is a growing opportunity to complement animal tissue work with acute and organotypic human brain slices obtained following surgical resection<sup>21,22</sup> as well as *in vivo* recordings from depth electrode-implanted patients.<sup>23</sup> However, there is a stark lack of information in some areas, for example, related to features of the neonatal brain that contribute to hypersynchronous activity, apart from changes in chloride ( $\text{Cl}^-$ ) gradients that render GABAergic transmission excitatory.<sup>24,25</sup> Early-life seizures are an important therapeutic target because many epileptic encephalopathies become apparent early in life. In particular, understanding the mechanisms underlying hypersynchronous firing in neonatal brain could lead to the development of therapies that are more effective for neonatal seizures as opposed to simply modifying the dosing of drugs that showed a positive signal in clinical trials in adults with epilepsy. Strategies could involve use of repurposed drugs, specific combinations of therapies, or the development of new therapies, noting, however, the substantial hurdles for bringing to market drugs for a pediatric population. Although the first uncontrolled trial of the repurposed drug bumetanide did not show efficacy,<sup>26</sup> this finding was controversial,<sup>27,28</sup> and the results of a subsequent blinded controlled trial of bumetanide is reported to be more promising (clinicaltrials.gov/NCT00830531). To this end, new genetic models of ultra-rare variants in genes capable of producing seizures and hyperexcitability may provide new models of mechanisms underlying development of an epileptic focus in neonatal animals. Indeed, multiple animal models of genetic epilepsies

show seizure activity at an early age, providing an opportunity to study epilepsy in the developing brain.

The role of inflammation has been increasingly recognized in a wide range of neurological diseases, including epilepsy and status epilepticus.<sup>29-31</sup> Neuroinflammation can impact network excitability in several ways, including activating microglia, reshaping synaptic input, and altering ion channel function. Thus, there is the potential to explore anti-inflammatory therapies for use in conjunction with conventional ASMs in the chronic therapy of epilepsies that are thought to be inflammatory in nature, such as Rasmussen encephalitis.<sup>32</sup> In addition, the utility of some treatments for seizure categories not conventionally believed to be related to inflammatory mechanisms should be explored. This has the potential to perhaps reduce the refractory rate, or increase seizure control, for some groups of patients.

There is an emerging appreciation of autoimmune encephalitis<sup>33</sup> that involves antibodies against epitopes in proteins that control neuronal excitability, such as the NMDA receptor,<sup>34</sup> GAD65,<sup>35</sup> and GABA<sub>B</sub> receptor subunits.<sup>36,37</sup> Patients with antibody-mediated encephalitis often exhibit nonconvulsive seizures, in addition to memory loss, psychiatric symptoms, and other features. For some epitopes, preclinical data validate the immunoglobulin G fraction as causative for seizures. Treatment with immunotherapy can be effective, but additional therapeutic strategies are needed.<sup>36,38</sup> The full extent of this clinical condition is just now becoming appreciated, and it remains almost certainly underdiagnosed at this point. Thus, future work should focus on earlier recognition of these presentations and early and robust diagnosis in order to achieve potentially effective treatment before the development of irreversible sequelae of neuroinflammation.

### Genetic Advances

An important consequence of the many genetic advances that are transforming clinical neurology<sup>39</sup> is their ability to suggest new animal models to investigate the underlying disease mechanisms, including compensatory mechanisms that can contribute to a seizure focus.<sup>40</sup> Such models are relevant to genetic human epilepsies and serve as an important complement to the acquired models of focal epilepsy (eg, pharmacologically induced seizure models) that have become the mainstay for development of *in vivo* models of chronic recurring seizures. Animal models of single-gene defects offer an opportunity to evaluate windows for therapeutic intervention in patients who have these specific variants, with the possibility that some therapies will be more broadly applicable to multiple epilepsies. In addition, such models offer a new opportunity to study common mechanisms that underlie maladaptive plasticity and can lead to generation of a seizure focus. Novel gene expression programs may be triggered by genetic deficiencies that engage similar mechanisms, and understanding these might allow better understanding of antiepileptic drug utility.<sup>40</sup> In this respect, the intersection of gene expression data sets may inform key pathways that establish seizure foci regardless of the initial genetic defect driving seizures. In addition,



genetic animal models can facilitate the evaluation and validation of strategies such as antisense oligonucleotides, gene replacement, and gene augmentation. The success of new genetic treatments of spinal muscular atrophy with intravenously delivered gene replacement via adeno-associated viral vector in very young infants<sup>41</sup> has created hope for many patients that these therapies can correct other neurological conditions, stimulating work on this problem in academia and, importantly, in industry. Thus, there are actionable opportunities for genetic therapies for epilepsy on the horizon.

In addition to the value of new models suggested by genetic analysis, there are several opportunities to exploit advances in diagnostic and therapeutic genetic approaches. There are now multiple examples of strategies one could use to develop gene therapy employing viral vectors to treat focal and generalized epilepsies in animal models in which a missense variant or truncating mutation has modified the function of a target gene or reduced the gene dose.<sup>42</sup> Other innovative uses of gene therapy include introduction of potassium channels that could reduce excitability, as well as engineering cells to release neuroactive molecules that can counteract excessive excitability.<sup>43,44</sup> As more animal models are developed for different genes, there will be opportunities to test fundamental approaches that supplement underexpressed alleles or proteins with reduced function, as well as editing gene approaches to correct identified defects. These strategies will require demonstration of utility in animals with measurable defects, and the results will speak to the important question in epilepsy around whether symptoms are driven by the genetic defect, are a feature of maladaptive compensation, or reflect some combination of both. That is, there is a need for proof-of-concept data for oligonucleotide and antisense therapies for application in the treatment of genetically defined monogenic epilepsies, as well as data on effectiveness of the timing of treatment in the context of the development of a seizure focus. Advances are needed in genetic therapy using virus delivery vectors that are already approved for other payloads and access both brain and spinal cord following intrathecal administration. The rare genetic epilepsies might provide a test case for intervention, which can be evaluated in iPSC-based models *in vitro*, organoids derived from iPSC cells, and animal models now.

One opportunity that the accessibility of multiple new genetic models of human variants associated with epilepsy offers is evaluation of repurposed drugs. This requires a comprehensive functional evaluation of the effects of rare variants *in vitro*, which for ion channels is accessible. Functional evaluation of drug sensitivity of variant proteins will inform potential use of therapeutics, as will knowledge of the nature of the net functional effects as either gain of function or loss of function, or indeterminate.<sup>45-49</sup> Genetic models—from cellular models to zebrafish and mouse models—harboring variants can then be screened for actions of Food and Drug Administration (FDA)-approved medications for efficacy in reducing electroencephalogram abnormalities and seizures<sup>46,50,51</sup> as a step toward using pharmacological treatments. If the models capture patient-relevant features of epileptogenesis, early

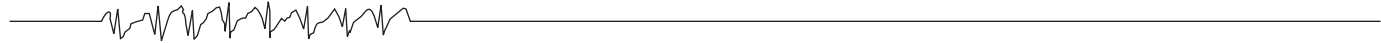
treatment within a vulnerable window might have long-lasting consequences.

In addition to these pharmacological approaches, bioinformatics coupled with large-scale data sets have driven the development of computational resources<sup>52,53</sup> that can suggest candidate drugs in the FDA library from patterns of changes in gene expression. Moreover, evaluation of multiple drugs in multiple models might identify candidate drugs as add-on therapies that could be used more broadly than for just for rare genetic conditions. Indeed, a large number of epilepsy models have been or are being made from various genes identified in patients with rare epilepsies (eg, sodium channels, potassium channels, post-synaptic ligand-gated ion channels, synaptic proteins), which will provide patient-relevant models in which to assess new pharmacological strategies. These same models can be used to understand developmental compensation, transformation of the foci with time, and pharmacological sensitivity. It seems likely that some compensatory mechanisms will be shared across these different models and may inform treatment of refractory epilepsy. In addition to rodent models, use of companion models and organisms (fly, zebrafish, mice, iPSC-derived neuronal cultures, and organoids) could provide faster and more efficient drug screening<sup>43</sup> as well as evaluation of compensatory mechanisms.

The advances in genetic analysis could also expand our understanding of acquired epilepsies and yield insight into whether persons with genetic predispositions may be at greater risk and merit more aggressive treatment and management. This will require concerted effort to capture genetic information from patients with acute events that lead to seizures or increase seizure risk. With a sufficient sample size, some common polygenic factors might emerge, suggesting genes or genetic patterns that imply risk.<sup>6</sup> In some cases, one might consider treating the predisposition if it can be identified as the first step to gain adequate seizure control before considering, for example, epilepsy surgery. This same form of analyses could be applied to traumatic brain injury, stroke, hypoxia, and other insults that enhance the likelihood of future seizures.

## Refractory Epilepsy

About one-third of patients with epilepsy are in part or fully refractory to treatment, creating an enormous medical, social, and economic burden. Thus, an essential aspect of any future prioritization is the need to develop new or improve existing antiseizure therapies for patients with refractory epilepsy. Efforts should include analysis of sequencing data for patients who fail to show adequate improvement following surgical intervention to determine whether there are shared risk factors, as well as those who successfully respond. Approaches that deserve consideration in this regard include conventional drug development, selection of surgical patients, and genetic analysis of both responsive and refractory patients. Toward this end, several new drugs have entered clinical use following FDA approval, including cannabidiol for Dravet and Lennox-Gastaut syndromes,<sup>54,55</sup> nasally administered midazolam for seizure clusters,<sup>56</sup> stiripentol for Dravet syndrome,<sup>57</sup> and



everolimus for seizures in patients with tuberous sclerosis complex.<sup>58</sup> In addition, new treatment approaches for specific epilepsies are under investigation with novel or disease-specific targets, including AMPA receptors containing the TARP $\gamma$ 8 subunit, expressed predominantly in the temporal lobe and of potential relevance to mesial temporal lobe epilepsy<sup>59</sup>; KCNQ (Kv7) potassium channels implicated in KCNQ2 developmental and epileptic encephalopathy<sup>60</sup>; and serotonin systems, representing a target of fenfluramine, which have been reported to cause seizure reduction in patients with Dravet syndrome.<sup>61</sup> New routes of drug administration are also being explored.<sup>62</sup> It will be important to carefully evaluate the utility of these new medications in refractory epilepsy beyond the initial indications for which they are tested or approved.

In addition to new medications, more effort is needed to understand the mechanisms of pharmacoresistance in order to overcome refractoriness to ASMs. To this end, new animal models together with humanized models *in vitro* based on genetic data may provide an opportunity to explore mechanisms of resistance for those specific models with clear seizure phenotypes for which the patient is known to be refractory to treatment with conventional anticonvulsants. Work in this area would benefit from integration of information about new targets into existing efforts to develop new medications that are effective against refractory seizures. In addition to traditional targets such as ion channels, neurotransmitter receptors, and neurotransmitter transporters, important targets include mTOR and related pathways, the extracellular matrix, oxidative stress, anti-inflammatory pathways, neurosteroid systems, microRNAs, and epigenetic targets include histone deacetylase.<sup>30,31,63-67</sup> Cell replacement strategies to introduce engineered cells that can support or release neuroactive substances and oligonucleotide approaches to regulate specific genes for therapeutic gain are also opportunities to identify new ways to treat refractory epilepsy. Moreover, clarification of the mechanisms underlying the ketogenic diet might identify metabolic and lipid targets that are relevant, the role of the gut microbiota,<sup>68</sup> and allow a “ketogenic diet in a pill” treatment strategy for refractory epilepsy.

### Real-Time Management of Seizures

Efforts have been made for decades to predict when seizures will occur and provide an immediate intervention to either prevent or terminate the seizure.<sup>69</sup> These efforts rely on a range of recording devices, computational algorithms to identify at-risk periods, and active response in the form of electrical/optical stimulation or administration of a drug. Although there has been steady progress with these strategies over the decades, many approaches are maturing to the point where they seem poised to provide a workable and effective therapy for a larger number of patients.<sup>70</sup> Indeed, the introduction in 2013 of an FDA-approved closed loop device that detects seizures and aborts them by deep brain stimulation has spawned many efforts to refine stimulation parameters for better seizure control.<sup>71</sup> New seizure prediction algorithms<sup>8</sup> as well as new

devices may allow intravenous injection or even direct infusion of antiseizure agents into the brain at the onset of or immediately before a seizure is predicted.<sup>72</sup> This approach has the capacity to harness the utility of proven pharmacological treatments without the side effects of chronic exposure to drug in blood and brain. Taken a step further, introduction of active drug locally into the epileptic focus could provide more selective treatment of certain epileptic conditions, including refractory epilepsies, localization-related epilepsies, and status epilepticus. Increasing power of computational algorithms<sup>7</sup> should allow enhanced ability to predict seizures from multiple streams of data, including electrical recordings and peripheral readouts. In addition, miniaturization of devices can improve the ability to deliver electrical, light, or pharmacological stimuli to specific regions both inside and outside of the central nervous system. The emergence of new animal models of genetic epilepsies provides another opportunity to test detection and seizure interruption strategies in homogeneous models that share some basis with human epilepsy and thus might provide robust data that can be translated to patients harboring these variants. A range of models might stimulate improvements in the low signal to noise ratio in seizure prediction and in the abortion of seizures, such as evaluation of new biomarkers that change prior to seizure initiation<sup>73</sup> and consideration of circadian rhythms.<sup>74</sup> Ultimately, these systems need to be suitable for self-management in the home and other nonmedical settings in order to improve adherence and efficacy.

Taken to its logical albeit futuristic conclusion, one might envision a paradigm shift from ASMs in the form of multiple doses of a drug per day and steady-state blood levels (with attendant side effects) to delivery systems that provide anticonvulsants to the brain at the site they are needed and only when they are needed, improving the quality of life of the patient. Further, each patient’s treatment would be customized based on genetic and molecular profiles. This form of precision medicine would eliminate the need for chronic and systemic nonspecific and side effect-laden pharmacotherapy, improving efficacy and possibly reducing the development of pharmacoresistance.

### Future Directions: Challenges and Opportunities

The genetic, technical, and conceptual advances discussed above provide new opportunities for basic research as well as clinical interventions. These advances offer a chance to view the epilepsies from a different perspective and address long-term problems that have until now have been difficult to progress.

#### Authors’ Note

The opinions expressed in this publication are those of the author(s) and do not necessarily reflect the views of the NIH or the AES.

#### Acknowledgments

The authors thank Dr Ray Dingleline for critical comments on the manuscript. In addition, they acknowledge the helpful feedback from the Epilepsy Leadership Council and other stewards of the NINDS/



AES Epilepsy Research Benchmark Stewards committee during the formulation of this manuscript.


### Declaration of Conflicting Interests


The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: S.F.T. is a PI on research grants from Janssen and Allergan to Emory University; is a paid consultant for Janssen; is a member of the SAB for Sage Therapeutics, the GRIN2B Foundation, and Cure-GRIN; is cofounder of NeurOp Inc; receives licensing fees and royalties for software; and is a co-inventor on Emory University-owned Intellectual Property that includes allosteric modulators of glutamate receptor function. D.D. receives salary support from the Commonwealth of Pennsylvania Department of Health, Pediatric Epilepsy Research Foundation, and The Epilepsy Study Consortium and is an investigator on research grants awarded to CHOP from the Commonwealth of PA Department of Health, Zogenix, Greenwich Biosciences, UCB, Brain Sentinel, Neurelis, Q-State, USL, Aquestive, Bio-Pharm, Insys, SK Life Sciences, and Encoded Therapeutics. D.C.H. is a coinventor on US patent no. US 9,803,200 B2, "Inhibition of microRNA-134 for the treatment of seizure-related disorders and neurologic injuries." A.P. serves on the scientific advisory board of Tevard and has a spouse/partner who receives a salary from Sanofi Genzyme. H.C.M. is a member of scientific advisory boards for Lennox Gastaut Syndrome Foundation, Dravet Syndrome Foundation, and SPARK. M.A.R. is principal investigator on research grants to the University of California, Davis, from NINDS (U54NS079202, R25NS099170, U01NS112102) and Mallinckrodt Pharmaceuticals; has served as a consultant to Eisai, West Therapeutics Development, Xenon Pharmaceuticals, and Aquestive Therapeutics; is a member of the board of directors of Epalex; is a member of the scientific advisory board of Zynerva Pharmaceuticals; and is named as an inventor of patents and patent applications assigned to the Regents of the University of California.


### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the NIH R35NS111619 (S.F.T.), R01 NS069605 (H.C.M.), R01NS040109 (K.S.), R01NS034700 (K.S.), R21NS096948 (K.S.), and R37NS077908 (K.S.) and grant W81XWH-15-2-0069 from CURE and DOD (K.S.), the Science Foundation Ireland (D.C.H., grant numbers 16/RC/3948, 13/IA/1891, and 11/TIDA/B1988), European Regional Development Fund and by FutureNeuro industry partners (D.C.H.), the Health Research Board Ireland HRA-POR-2013-325 (D.C.H.), the European Union Seventh Framework Programme FP7/2007-2013 grant agreement n° 602130 (D.C.H.).

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