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SPECIAL REPORT

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Antiepileptogenesis and disease modification: Progress, challenges, and the path forward—Report of the Preclinical Working Group of the 2018 NINDS-sponsored antiepileptogenesis and disease modification workshop

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Abstract

Epilepsy is one of the most common chronic brain diseases and is often associated with cognitive, behavioral, or other medical conditions. The need for therapies that would prevent, ameliorate, or cure epilepsy and the attendant comorbidities is a priority for both epilepsy research and public health. In 2018, the National Institute of Neurological Disease and Stroke (NINDS) convened a workshop titled "Accelerating the Development of Therapies for Antiepileptogenesis and Disease Modification" that brought together preclinical and clinical investigators and industry and regulatory bodies' representatives to discuss and propose a roadmap to accelerate the development of antiepileptogenic (AEG) and disease-modifying (DM) new therapies. This

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report provides a summary of the discussions and proposals of the Preclinical Science working group. Highlights of the progress of collaborative preclinical research projects on AEG/DM of ongoing research initiatives aiming to improve infrastructure and translation to clinical trials are presented. Opportunities and challenges of preclinical epilepsy research, vis-à-vis clinical research, were extensively discussed, as they pertain to modeling of specific epilepsy types across etiologies and ages, the utilization of preclinical models in AG/DM studies, and the strategies and study designs, as well as on matters pertaining to transparency, data sharing, and reporting research findings. A set of suggestions on research initiatives, infrastructure, workshops, advocacy, and opportunities for expanding the borders of epilepsy research were discussed and proposed as useful initiatives that could help create a roadmap to accelerate and optimize preclinical translational AEG/DM epilepsy research.

KEYWORDS

acquired epilepsy, animal model, comorbidity, epilepsy, genetic epilepsy, translation, treatment

Key Points

- The development of new treatments to prevent, cure, or ameliorate epilepsy and comorbidities is a priority in epilepsy research.
- The 2018 NINDS workshop discussed issues relevant to accelerating the development of antiepileptogenic (AEG) and disease-modifying (DM) therapies.
- This report summarizes the discussions of the preclinical group on opportunities and challenges of preclinical models and strategies used in testing AEG/DM candidate treatments.
- A set of suggestions that could improve the productivity and translation of preclinical AEG/DM studies are outlined.

1 | INTRODUCTION

Epilepsy affects 50-70 million people worldwide and across the lifespan.[1,2] A third of people who have access to treatments for epilepsy fail to respond to available medical treatments. Epilepsy could be preventable in approximately 25% of people at risk, if effective treatments were available.[1] Preventable causes include traumatic brain injury (TBI), brain infections, perinatal insults, and genetic epilepsies. Furthermore, about 70% of people with epilepsy from low-income countries do not have access to treatments that could render them seizure-free. A majority of individuals with epilepsy are also faced with epilepsy-related comorbidities, including cognitive, behavioral, or other medical conditions that impact the quality of their lives.

The term epilepsy encompasses a large spectrum of distinct epilepsy syndromes and epilepsy types,[3,4] each distinguished by its own natural course and range of etiologies, networks and mechanisms implicated in its pathogenesis, associated comorbidities, and response profile to available treatments. There are numerous models of seizures and epilepsies[5] that have provided important insights on mechanisms, therapy targets, and candidate treatments for epilepsies and seizures. While epilepsy research has been very efficient in producing numerous antiseizure medications, these are symptomatic treatments. There is currently no available medical treatment that can prevent, stop, or ameliorate the course of epilepsies and related comorbidities. The need to develop effective and safe antiepileptogenesis (AEG), disease-modifying (DM), and/or epilepsy prevention treatments is considered a high priority in epilepsy research and care.[6] Parallel initiatives from various fronts have intensified efforts to agree on best practices, priorities, and best infrastructure to accelerate the path toward the development of AEG/DM or prevention treatments for epilepsies and improve infrastructure to support team or collaborative research (Table 1).

To update on and cross-fertilize these efforts, the National Institute of Neurological Disease and Stroke (NINDS) convened a workshop titled "Accelerating the Development of Therapies for Antiepileptogenesis and Disease Modification"

TABLE 1 Initiatives on funding or advancing AEG/DM preclinical studies

Initiative	Sponsor	Purpose
ETSP	NINDS (Division of Translational Research)	Identification of new therapeutic agents for the unmet medical needs in the epilepsies, including AEG, DM, and prevention
EpiBioS4Rx	NINDS	Center without walls (CWoW) for biomarker discovery and screening for therapies to prevent PTE
TAPTE	CURE Epilepsy and the US Department of Defense Psychological Health and Traumatic Brain Injury Research Program, award W81XWH-15-2-0069	Team Approach to the Prevention and Treatment of PTE
EpiXchange/ Epicluster	European Community, EBRA	Present major findings from European Community-funded collaborative projects on epilepsy and discuss challenges and strategies to bring epilepsy research closer to clinical application. Establish collaborative framework for coordinated actions of epilepsy research in Europe
ILAE/ AES Joint Translational Task Force	ILAE, AES CURE Epilepsy, Epilepsy Therapy project, Autism Speaks	Undertake initiatives to optimize epilepsy therapy development and translation to the clinics. Initiatives that have been undertaken include harmonization of vEEG studies, interpretation and seizure classification in animal models, systematic reviews, preclinical CDEs for epilepsy, infrastructure development
Translational Research Programs	NINDS (Division of Translational Research)	Translational programs at NINDS were established with the goal of helping to ensure project preparedness in the early stages and resources to develop small molecules, biologics and neural devices are available for promising AEG/DM interventions and biomarkers from academic investigators and small businesses. Program details depending on project stage and modality are further described: https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Translational-Research

Abbreviations: AEG, antiepileptogenesis; AES, American Epilepsy Society; CDE, common data elements; Citizens United for Research in Epilepsy doing business as CURE Epilepsy; CWoW, Center Without Walls; DM, disease modification; EBRA, European Brain Research Area; EpiBioS4Rx, Epilepsy Bioinformatics Study for antiepileptogenic therapy; ETSP, Epilepsy therapy Screening Program; ILAE, International League Against Epilepsy; NINDS, National Institutes of Neurological Disorders and Stroke; PTE, posttraumatic epilepsy; TAPTE, Team Approach to the Prevention and Treatment of PTE; vEEG, video encephalography.

(Bethesda, MD, August 2018). The overall goals included (a) identifying optimal populations of individuals with epilepsy or at risk for developing epilepsy for the investigation of new AEG and DM therapies; (b) aligning relevant animal models to these populations and identifying common pathways; (c) suggesting steps needed to develop and validate translational biomarkers; and (d) provide and/or develop strategies to address barriers and challenges in order to accelerate development of new therapies. An additional goal was to inform the NINDS Epilepsy Therapy Screening Program as it develops new preclinical workflows to identify potential AEG and DM therapies. The workshop was organized into subgroups: Preclinical Science; Regulatory and Industry; Clinical; and Biomarkers and Translational Science. Each group worked to identify gaps and determine the goals, strategies, outcomes, and next steps to advance therapy development. This report summarizes the

presentations and discussions of the preclinical science working group (WG) with the goal to reevaluate current progress and strategies, identify areas for improvement, and propose improvements in infrastructure, practices, and research strategies that could accelerate the path toward the development of AEG/DM therapies. In this report, we considered as AEG the treatments that prevent or ameliorate the development or progression of epilepsy and their effects are not simply attributed to antiseizure effects of the treatments (Figure 1). DM therapies can be AEG or prevent, cure, or ameliorate the development and progression of epilepsy comorbidities.

2 | UPDATES ON RECENT INITIATIVES ON PRECLINICAL EPILEPSY TRANSLATIONAL RESEARCH

The NINDS sponsored a 2010 workshop entitled "Antiepileptogenesis and disease modification: alignment and validation of clinical targets and pre-clinical models." The overall goal of the workshop was to develop a collaborative "proof-of-concept" experimental framework for translation of therapeutic interventions to prevent or modify disease progression in the epilepsies. The preclinical issues discussed during the workshop were that few antiepileptogenic strategies had been systematically tested in multiple models and the need to improve alignment of preclinical studies with clinically feasible assessments. Discussions of the preclinical working group at the workshop identified the need to better understand the critical events and time course of changes following a brain insult that lead to the development of epilepsy and cost-effective ways to monitor seizure endpoints over the long term in animal models. Additional suggestions included the need to develop standards for carrying out preclinical studies and evaluating the reliability and feasibility of using animals to study epileptogenesis that are predictive and reliable models of the human condition. Lastly, there was a call for accelerated programs to identify new drugs with antiepileptogenic properties and an increased collaboration between investigators. Key advancements toward the preclinical suggestions since the 2010 workshop are listed in Table 1. These include the European Community and CURE Epilepsy-funded collaborative, team science initiatives summarized below. Initiatives for harmonization of methodology and reporting outcome measures are being advanced by the joint International League Against Epilepsy (ILAE)-American Epilepsy Society (AES) translational task force efforts described below. NINDS-funded programs to accelerate the identification of new AEG and DM therapies are described under Strategies and Progress

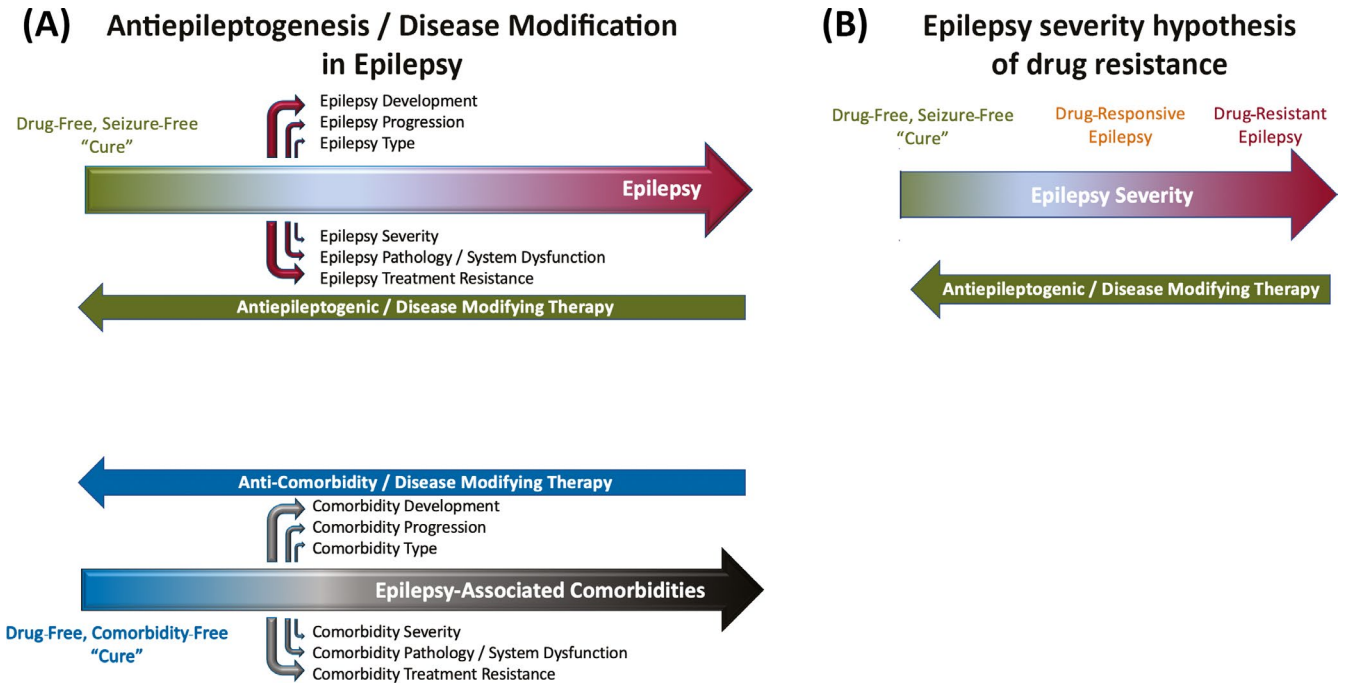

FIGURE 1 Antiepileptogenesis, disease modification, and drug resistance in epilepsy. A, Disease modification (DM) may lead to prevention, cure, or amelioration of epilepsy [ie, antiepileptogenesis (AEG)] or associated comorbidities (ie, anticomorbidity DM therapy) through actions that cannot be simply attributed to antiseizure effects of the treatment. AEG and DM treatments can alter the development, progression, type, severity, pathology and system dysfunction, or treatment response of epilepsies and associated comorbidities. B, Drug resistance in epilepsy has been proposed to be a manifestation of the severity of the intrinsic epilepsy network.[42] Alternative hypotheses on mechanisms of drug resistance have been published.[41] An AEG/DM therapy may mitigate drug resistance, cure, or prevent epilepsy[54]

(C4-C5) and include refocusing the Epilepsy Therapy Screening Program (ETSP) toward AEG and DM screening and a Center without Walls (CWoW) project bringing together an international team of investigators to identify biomarkers and therapies for preventing posttraumatic epilepsy (PTE).

2.1 | Joint translational initiatives of the International League Against Epilepsy (ILAE) and the American Epilepsy Society (AES)

In a joint initiative to optimize and accelerate preclinical epilepsy therapy development, the ILAE and AES, with the support of NINDS and nonprofit organizations including CURE Epilepsy, Epilepsy Therapy Project and Autism Speaks, organized the first joint international translational workshop in London, UK (2012).[6,7] The three priorities in the vision to transform epilepsy research and care were the development of AEG and DM treatments and treatments for drug-resistant seizures and comorbidities.[6] The ILAE/AES Joint Translational Task Force spearheaded an international collaboration of expert working group members who developed proposals for harmonizing the methodology and interpretation of video-electroencephalography (vEEG) studies in rodent models (TASK1),[8-13] undertook a systematic review on outcome measures in preclinical epilepsy studies (TASK2),[14] created preclinical epilepsy research common data elements (CDEs) to improve across-studies comparisons, study reporting, and collaborative research (TASK3),[15-21] and proposed infrastructure for multicenter preclinical trials for epilepsy therapy development (TASK4).[22]

2.2 | EpiXchange/Epicluster

EpiXchange was an initiative of seven large European Community-funded collaborative projects on epilepsy with the aim to bring together the excellence of epilepsy research in Europe for a conference in Brussels on May 23, 2018 (http://www.epixchange2018.eu/). The main goal was to present the major findings from these projects, to discuss the bottlenecks and strategies to move forward, and to bring research results closer to clinical application. The epilepsy research consortia that met in Brussels were DESIRE, EpimiRNA, EpiPGX, EpiCare, EPISTOP, EPITARGET, and epiXchange. Key themes of the conference were (a) genetics (development of novel treatment strategies based on optogenetics, gene, and stem cell therapies), (b) therapeutics (development of effective AEG therapeutics), (c) biomarkers (identification of new biomarkers in blood, peripheral organs, brain tissue, electrophysical, behavioral, and imaging data, in order to develop novel preventive strategies in at-risk patients), (d) biobanks and databases (integration of biobanks and databases into clinical care to facilitate preclinical research), and (e) comorbidities (exploration of the mechanisms underlying bidirectional relations between epilepsy and neurological comorbidities to reduce the high burden of comorbidities in epilepsy).[23] Following the epiXchange conference, the European Commission together with epiXchange partners organized a workshop in Brussels on May 24, 2018 ("Translating Research into Action – Shaping the Future of the Epilepsy Research") to discuss main achievements, challenges, and priorities in epilepsy research and to establish long-term strategies with a global approach. One of the immediate consequences of epiXchange was the launch of Epicluster (https://www.ebra.eu/epi-cluster/), which has the primary objective to establish a collaborative framework for the coordinated actions of epilepsy research in Europe, based around shared partnerships and research priorities.

2.3 | CURE Epilepsy Posttraumatic Epilepsy (PTE) Initiative

Several consortia-style projects have been initiated to study AEG and PTE which is a frequent and debilitating complication of TBI. For example, in 2018 CURE *Epilepsy* launched a multidisciplinary program with multiple investigative teams that aim to expand the knowledge of the types of injuries that predispose the brain to epilepsy, as well as develop new models and identify biomarkers to study epilepsy resulting from injury. CURE Epilepsy's PTE "Team Science" Initiative operates based on principles developed through its predecessor, the CURE *Epilepsy* Infantile Spasms Initiative,[24] and requires teams to collaborate in real time, share knowledge and scientific resources including samples, protocols, and models, and meet regularly via teleconference and face-to-face meetings to share progress. Teams also rapidly adapt scientific plans based on advice from Initiative advisors with a goal to "let the science drive the direction," thereby accelerating the path toward the development of AEG therapies (https://www.curepilepsy.org/signature_programs/post-traumatic-epilepsy/).

3 | STRATEGIES AND PROGRESS IN PRECLINICAL DEVELOPMENT OF AEG/DM TREATMENTS

3.1 | Disease prevention vs modification strategies for epilepsies

3.1.1 | Opportunities for AEG/DM therapies

While the development of an AEG intervention that effectively prevents or mitigates the development of epilepsy after

a brain insult, such as a TBI, would be of significant clinical value, the vast majority of patients present with established epilepsy. The opportunities for disease prevention therapies are much more limited, such as patients who are seen at the time of a known acquired brain insult (eg, TBI, stroke, CNS infection, or tumor) or babies/children carrying a known epilepsy genetic mutation (eg, in sodium channel SCN1A, tuberous sclerosis complex (TSC) genes TSC1 or TSC2) who have not yet manifested with epilepsy. Therefore, a DM therapy (DMT) that is effective in curing or reducing the severity of the epilepsy or attendant comorbidities would have immense clinical and societal benefits for these patients, reducing drug resistance, medication burden, comorbidities, disability, and mortality, and is one of the key "Grand Challenges" for translational research in the field.[6,25]

Because there is currently no medical DMT that can cure patients with epilepsy, patients are required to take symptomatic antiseizure medications (ASMs), with a frequency of 1-3 times per day dosing, in a regimen sustained for years, and often a lifetime. Not surprisingly, poor treatment adherence is common, and this is a common cause of seizure recurrence even in patients with drug-responsive epilepsies. Inadequate adherence to regular ASMs has been shown to be associated with increased death rates, injury, hospital admissions, and costs.[26,27] Also there is an increasing recognition of the long-term effects of chronic ASM use, including bone disease,[28] gait imbalance,[29] fractures,[30] obesity and metabolic syndrome,[31] and dermatological and hematological effects. Furthermore, because there are no medical curative therapies, women with epilepsy generally need to continue to take ASMs during pregnancy, which may carry an increased risk to the unborn child of birth defects, neurocognitive deficits, and even autism spectrum disorders.[32-34]

3.1.2 | Drug-resistant epilepsies

Despite more than 20 new ASMs being introduced into clinical practice over the past three decades, the incidence of drug-resistant epilepsy has essentially not changed, still affecting more than 30% of patients.[35,36] Drug-resistant epilepsy is associated with significant morbidity, including decreased quality of life, increased injury and hospitalization rates, higher medical and psychiatric comorbidities,[37] elevated death rates [including sudden unexpected death in epilepsy (SUDEP)],[38,39] and increased economic costs to society.[40] Several mechanisms contributing to drug resistance have been reported.[41] It has also been proposed that drug resistance in epilepsy is a manifestation of the intrinsic disease severity of the epileptogenic substrate[42] (Figure 1). Accordingly, a therapy that could reduce the severity of a person's epilepsy could potentially change (or modify) it from being drug-resistant to drug-responsive, with all the clinical, morbidity and mortality benefits that this would bring (Figure 1). The "proof-of-concept" for this is seen with epilepsy surgery, the only effective DMT that we currently have available in clinical practice. Successful epilepsy surgery involves the surgical excision of a sufficient amount of the epileptogenic network (zone) so that either there is a cure of the epilepsy (ie, no seizures, no drugs) or the seizures are now drug-responsive.[43] These outcomes are achieved in up to ~80% of patients who are "ideal" surgical candidates during a postoperative follow-up of 1-10 years, in whom all of the above-mentioned adverse associations of drug-resistant epilepsy, including psychiatric comorbidities and death rates, are significantly improved.[43-51] Unfortunately, less than 5% of patients with drug-resistant epilepsy are ideal candidates for epilepsy surgery because the epileptogenic zone is multifocal, bihemispheric, diffuse, generalized, or unable to be sufficiently localized.[52,53] Therefore, the challenge for the field of translational therapy development research for epilepsy and related disorders is to achieve effective DMT for drug-resistant epilepsy, or prevent its development, with nonmedical or cellular approaches.[54]

3.1.3 | AEG/DM treatment trials

Most preclinical and clinical research into DMT in epilepsy has focused on epilepsy prevention.[54] While there may be overlap in the cellular targets and interventions that are effective for AEG, other strategies may be required to mitigate the severity of an established epileptogenic network. Therefore, preclinical and clinical study designs that specifically address this are required. For preclinical studies, the intervention should be applied in true epilepsy models with the animals in the chronic epileptic stage manifesting chronic spontaneous seizures with a randomized, controlled study design with the endpoints analyzed by an operator blinded to the animals' treatment group.[6] Quantitating the seizures requires the utilization of chronic vEEG recordings,[11,55,56] which means that the infrastructure and cost of such studies is greater than traditional antiseizure drug screens using induced acute seizure models. Testing for cognitive and behavioral comorbidities should also be done, as an effective DMT may also mitigate these which are now considered an integral part of the epileptic disease.[57]

Both preclinical and clinical studies of DM in established epilepsy are likely to be less expensive, shorter, and more practical than preventative AEG studies. This is because epilepsy prevention studies usually require follow-up periods after the brain insult of weeks to months for animals, and a year or more for humans, before the epilepsy would be expected to develop. Furthermore, only a minority of patients is diagnosed with epilepsy following any brain insult, for example, ranging between 2% and 50% following TBI, depending

on its severity,[58-60] and therefore, a large number of subjects would need to be enrolled to demonstrate a meaningful effect to prevent epilepsy.[61] In contrast, a DMT trial in patients with established epilepsy could require shorter timeframe with less subjects needed to be enrolled. A standard drug-resistant epilepsy study design could be used, enrolling patients with frequent seizures (eg, average 4 per month) and treating for several months in an add-on randomized controlled trial design, but with the purported DMT stopped at the end of the treatment period and the patients followed for a sustained effect to reduce seizure frequency/drug resistance.

3.2 | AEG therapies for genetic epilepsies: present, future

3.2.1 | Opportunities

The most profoundly disabling of the medically intractable epilepsies are the early developmental and epileptic encephalopathies, which are characterized by lifelong intellectual disability and early-onset epilepsy. The severity of these epileptic encephalopathies can be disproportional to the severity of the genetic alterations that give rise to them. Many early epileptic encephalopathies arise from the alteration of a single base pair in a gene that is intolerant of such variance. These genes may be important in the anatomical development of the brain, such as Aristaless X-linked homeobox gene (*ARX)*,[62,63] or they may be functionally important, such as the presynaptic protein *syntaxin-binding protein 1* (STXBP1).[64] Because brain development is activity-dependent,[65] many genes may influence both the function and the development of the brain.

3.2.2 | Advances

The genetic revolution of neurology started with dramatic increases in diagnostic capacity, such that we can determine a genetic etiology in as many as 40% of early epileptic encephalopathies utilizing genetic sequencing that is becoming progressively more widely available.[66,67] The next wave of the diagnostic revolution will require solutions to significant big data problems—sequencing, storing, and analyzing the intronic DNA sequences that make up some 98% of our genetic information[68]; detecting and analyzing pathological epigenetic changes that affect gene expression[69]; and diagnosing somatic mutations.[70] Early genetic diagnosis may facilitate the use of treatments that prevent or ameliorate the course of genetic epilepsies or the identification of early biomarkers that could inform on prognosis or treatment implementation. Preventative use of vigabatrin, for example, in children with TSC before the onset of seizures, but after the detection of epileptiform EEG activities, delayed the onset of clinical seizures and reduced the risk for clinical seizures, infantile spasms, and drug-resistant epilepsy over a two years observation period.[71,72] Genetic diagnosis has also enabled the use of targeted therapies. In the EXIST-3 trial, the mTOR (mechanistic target of rapamycin) inhibitor everolimus reduced seizure frequency in TSC patients.[73] Promising effects of everolimus were also demonstrated for infantile spasms, hypsarrhythmia, and developmental outcomes in a small prospective observational study of four infants with TSC and infantile spasms.[74]

An even more exciting element of the genetic revolution has been the implementation of gene therapies for neurological diseases that were uniformly hopeless just a handful of years ago. Intrathecal oligonucleotide and viral vector-mediated gene replacement treatments for spinal muscular atrophy (SMA) have been the first to become widely available.[75] The availability of these therapies, and the need for early administration, has led in turn to the addition of focused genetic sequencing to newborn screening programs in many states.[76] Although SMA is not an epileptic disorder, the new treatments for this disorder have brought several of the therapeutic questions for epilepsy into sharper focus, such as oligonucleotide-induced alteration of gene expression for Dravet syndrome.[77]

3.2.3 | Challenges

Does the gene need to be replaced or suppressed? Dominant negative disorders, in which the abnormal gene product interferes with the normal gene product, are best treated by reducing the abnormal gene product at the level of DNA transcription or RNA translation.[78] Gain-of-function mutations are also less likely to be cured by increasing the expression of the normal gene product.[79]

When in life is the gene product necessary? Mutations in genes whose impact is primarily on early brain development may produce profound epileptic encephalopathies, but it is unclear that replacement of the gene product after birth will be useful.[62,63] Although it is tempting to give up on this class of gene disorders, there have been surprising improvements after late correction of such genetic disorders in preclinical studies.[80,81]

Where is the gene expressed? Getting the viral vector bearing the gene replacement machinery into the cells in most need of gene replacement can be a significant technical challenge. For SMA, the lower motor neurons are in close proximity to the surface of the spinal cord, so intrathecal administration has been successful. This might not be true for neurons in deep cortical layers or the thalamus. For such neurons, systemic administration may be necessary, but this brings its own challenges in terms of amount of virus needed, and systemic reactions to gene replacement.[82]

How tightly regulated is the gene product? Current gene therapies for neurological diseases, including SMA[75] and Giant Axonal Dystrophy,[83] have focused on what used to be called "housekeeping" genes that to our knowledge are not directly involved in signal transduction. These genes can be replaced or their translation enhanced without worrying too much about the precise level of protein that results. In contrast, for gene products that involve signal transduction, such as the ion channels whose genetic mutations are responsible for many of the early epileptic encephalopathies, it may be much more difficult to get the proper balance of protein expression. This is particularly true for genes whose protein products are regulated by neuronal activity. For these genes, viral vector-mediated expression of corrected gene may not be sufficient; rather, repair of the gene itself may be required. Gene repair, as opposed to replacement, is still in preclinical stages, but this area has also seen many recent revolutionary technological advances (Clustered Regularly Interspaced Short Palindromic Repeats: CRISPR).[84]

In the next years, genetic therapies will change many more diseases like SMA from catastrophic menace to the never-seen subjects of newborn screening. With money, luck, and effort, many of those diseases will be the early epileptic encephalopathies.[77]

3.3 | AEG strategies for acquired epilepsies

Acquired epilepsies develop after acute brain insults or congenital or acquired structural abnormalities. Although various causes for acquired epilepsies have been identified, the exact mechanisms that induce epileptogenesis and seizures remain poorly understood for most epilepsies. In spite of the diversity of the initial causes, several commonalities exist in epileptogenic processes, potentially representing shared pathogenic mechanisms.[85] The majority of experimental studies were carried out in adult rodent models of de novo status epilepticus or neurotrauma. More recently, emerging models of pediatric acquired epilepsies and CNS infections are providing further insights into common mechanisms of developmental epileptogenesis.[86-88]

Commonalities in epileptogenic processes encompass a broad spectrum of cellular and functional changes in glia, neurons, and cell components of the blood-brain barrier (BBB) that may cause, influence, or modify the clinical course of the disease. Notable examples include (a) the phenotypic cellular changes in astrocytes and microglia, in particular the induction of inflammatory pathways with concomitant release of ictogenic cytokines and danger signals, (b) oxidative stress, (c) brain-derived neurotrophic factor (BDNF)-tyrosine receptor kinase B (TrkB) signal induction, (d) mTOR overactivation, (e) altered neurogenesis, and (f) BBB dysfunction contributing to maladaptive plasticity and excitatory synaptogenesis and epigenetic and transcriptomic modifications in sets of genes resulting in acquired channelopathies.[86] In animal models of epileptogenesis, these mechanisms in concert contribute to establish a dysfunctional *glial-neuronal-vascular* network in susceptible brain regions, which underlies the generation and perpetuation of a seizure focus. Since several of these mechanisms initially discovered in preclinical models were substantiated in surgically resected or autoptic human epilepsy *foci*, they may represent an invaluable source of potential targets for novel treatments. Animal models have also shown commonalities in seizure propagation pathways beyond the initial focus (eg, limbic and cortico-thalamic circuitries) which may guide network-targeted therapeutic interventions.[85]

However, in spite of apparently similar inciting events, epilepsy is not diagnosed in the majority of patients, thus calling into play the role of individual homeostatic responses, counteracting the establishment of an epileptogenic network, and coexisting risk factors, which might influence whether a certain brain injury can be epileptogenic or not.

A recent conceptual view, based on experimental and clinical findings, proposes that epileptogenesis is a continuum process that underlies both the brain propensity to generate spontaneous seizures and the progression of the disease after its clinical onset.[89] For example, patients, and animal models, may experience over time an exacerbation of the number or severity of seizures, and drug resistance or neurological comorbidities may develop adding a further burden to the patient. This novel view of epileptogenesis has key therapeutic implications: It broadens the therapeutic window for medical interventions beyond the prevention of epilepsy onset and promotes the search for drugs that may favorably modify the disease and significantly alleviate the symptoms. The intention of current research, however, is to overcome the mere symptomatic control of epileptic seizures and the comorbidities by discovering novel treatments that modify the disease by acting on key pathogenic mechanisms. If successful, this attempt would result in the conversion of an active epileptogenic network into a less active or silent one (eg, by finding treatments that provoke a permanent increase in seizure threshold). Whether similar or different mechanisms underlie both—early and late—components of epileptogenesis is a matter for further investigation. In support for some common mechanisms operative in both phases, there are animal studies showing that anti-inflammatory or antioxidant drugs, either administered before or after the onset of epilepsy, can stop seizure progression and mitigate the comorbidities.[90-94] These beneficial effects persist after the treatment is stopped, thus denoting that a lasting disease modification effect has occurred.

In summary, the overall hypothesis and future challenge is that determining the degree of molecular/cellular and seizure networks overlapping among the epileptogenic processes ignited by differing inciting events, and during the disease

course, may guide network-level interventions for disease modifications in acquired epilepsies. The complexity and dynamics of epileptogenesis mechanisms reflect a disturbed network of interactions rather than alteration of a single molecular component or a set of neurons; therefore, combinations of drugs targeting more than one mechanism ("network pharmacology")[95] may be more effective than single treatments for counteracting the pathologic process. Serial therapy with drugs targeting different processes may be necessary as part of a combination therapy approach. Repurposing of approved drugs with relevant antiepileptogenesis pharmacologic mechanisms and known side effect profiles may be eligible and should be explored. Of note, combination therapy has complexities for potential pharmacokinetic (PK) interactions, for determination of the therapeutic windows for optimal pharmacodynamic effects, as well as potential toxic interactions. Alternatively, but not mutually exclusive, differential gene expression analysis and systems biology approaches in experimental and human epileptogenic tissues may lead to the identification of nodal points of control for common epileptogenic networks thus offering new potentially druggable targets [eg, Nrf2 (nuclear factor erythroid 2–related factor 2), Sestrin 3, miRNAs].[96-98]

We should also take into consideration the interindividual variations in disease-driving mechanisms and substrate heterogeneity that would allow testing a therapy on people with the same underlying epileptogenic causality. This concept implies the development of biomarkers for patient stratification which are still lacking.[99] A working group on Biomarkers for AEG and DM participated in the workshop and have provided a summary report on those efforts.[100]

A more systematic comparison among the animal models (eg, status epilepticus, neurotrauma, stroke, central nervous system (CNS) infection) and analysis of corresponding human brain tissue is warranted for further validation and identification of common mechanisms of epileptogenesis and for targeting them with therapeutics in at-risk patients.

3.4 | EpiBioS4Rx CWoW: PTE prevention

TBI can be the likely etiology in ~20% of individuals with acquired epilepsy. PTE occurs in 2%–50% of people experiencing TBI,[60] and the risk is higher after severe TBI. TBI can be easily identified, providing an opportunity to develop and stage biomarkers and therapeutic interventions for PTE. EpiBioS4Rx or *Epilepsy Bioinformatics Study for antiepileptogenic therapy* (https://epibios.loni.usc.edu) is an international center without walls (CWoW) NINDS-funded project that aims to identify novel therapies to prevent PTE through rigorous preclinical testing in multicenter studies (project 2)[101] and identify and validate predictive and clinically translatable biomarkers for PTE development (projects 1 and 3) and treatment response (project 2) that could be used to select vulnerable populations in both preclinical and clinical studies.[102,103] Selection of candidate treatments is also informed by pharmacokinetic/pharmacodynamic modeling, tests for target relevance and modification, efficacy and tolerability, in preparation for a powered multicenter blinded, randomized and vehicle-controlled preclinical AEG trial in the lateral fluid percussion injury PTE model.[104-106] In preparation for a larger clinical study, project 3 establishes an international network of clinical centers capable of performing rigorous clinical trials in PTE.[107] To anticipate the special challenges in epilepsy prevention trials, a public engagement core was created to provide education and participatory action research, encouraging the involvement of consumers and consumer organizations but also incorporating the consumer's perspective and expectations in the clinical trial planning.[108] To enable the collection and analyses of "big data" collected, EpiBioS4Rx also plans for open and shared resources for the epilepsy community for data repositories and analyses.[109]

3.5 | NINDS Epilepsy Therapy Screening Program (ETSP)

The ETSP is a NINDS-funded, preclinical screening program with a mission to facilitate the discovery of new therapeutic agents that address the unmet medical needs in epilepsy. The program provides screening of investigational agents in a battery of rodent seizure and epilepsy models at no cost to domestic and international participants. Recently, Working Groups commissioned by the National Advisory Neurological Disorders and Stroke (NANDS) Council reviewed the program and recommended the program focus on identifying compounds that address areas of unmet medical needs including drug-resistant epilepsy, DM and disease prevention. The ETSP initiated screening to identify potentially AEG or DM investigational agents utilizing two rodent models of post–kainic acid (KA) status epilepticus–induced epilepsy. The first is a rat model of systemically administered KA-induced epilepsy develops behavioral seizures following a latent period that are quantitated using continuous video-EEG monitoring. A mouse model of focal KA injection into the hippocampus (intrahippocampal KA model) that develops spontaneous hippocampal paroxysmal discharges (HPDs) measured electrographically is also utilized by the program. Investigational agents can be administered following the onset of KA-induced status epilepticus, during the latency period or during the spontaneous seizure or HPD phase to assess the effect of the investigational compounds on preventing or modifying epilepsy following compound administration. The ETSP continues to evaluate other potential models of epilepsy for assessing investigational agents for disease prevention and modification and actively seeks

input from an established External Consultant Board (ECB) and the epilepsy research community through workshops and other scientific forums. Additional programs were established in the NINDS Division of Translational Research that can help further advance promising interventions into preclinical and early clinical development (Table 1).

4 | OPPORTUNITIES, CHALLENGES, AND THE PATH FORWARD

The breakout session of the preclinical WG discussed the opportunities and challenges for preclinical AEG target discovery and treatment trials (Table 2) with the ultimate goal to prioritize a set of proposals to accelerate the path toward successful preclinical AEG trials (Table 3).

4.1 | Models of epilepsies in therapy development

There is an abundance of preclinical epilepsy or seizure models that offered a wealth of information on etiologies, contributing mechanisms and therapy targets, age-, sex-, or region-specific factors, inherent biological or extrinsic variables affecting the manifestations and outcomes of seizures or their treatments, enabling precision medicine. A variety of chemical, physical, or genetic induction methods, electrical or other means of neuromodulation have been used to enrich study cohorts with animals developing epilepsies. Induced models can be "*etiology-relevant*" to specific etiologies seen in human epilepsies, for example, genetic models or models of PTE. Others may reproduce phenotypic features or pathologies that characterize certain epilepsies, without necessarily faithfully modeling the etiologies known to occur in humans. Etiology-relevant animal models may facilitate the development of rational, etiology-driven therapies that enable precision medicine. However, many epilepsy syndromes have recognizable electroclinical features but diverse or multifactorial etiologies or pathologies, for example, epileptic spasms[110] or many focal-onset epilepsies. The identification of *common pathways or pathologies* may help design AEG treatments with broad efficacy for a more etiologically diverse population of epilepsy patients. For example, the use of mTOR inhibitors for genetic epilepsies, such as TSC-associated epilepsies, has led to successful treatment trials in both animal models and humans, but also expanded their use to nongenetic etiologies of epilepsy.[73,74,111-114] Models may also share characteristic phenotypes that permit *phenotypic screening* (see strategies).

In a third of individuals with epilepsy, etiology is unknown. In induced animal models, it is often difficult to dissociate the impact of induced from the naturally occurring epileptogenic pathologies. Naturally occurring epilepsy has been documented and amplified by inbreeding of animals, such as in the inbred Genetic Absence Epilepsy Rats from Strasbourg (GAERS) or the WAG/Rij rats,[115,116] the photosensitive epilepsy in Papio papio baboons,[117] or in veterinarian client populations with epilepsy.[118] However, there are currently no systematic studies on incidence, types, and features of naturally occurring epilepsies in rodents, including those of nongenetic etiology, focal-onset, or drug-resistant epilepsies, that could be used to validate the relevance of pathologies or mechanisms identified in the induced models. It was suggested that studies on the natural history and incidence of epilepsies in animal strains used in modeling epilepsies would be helpful in discerning induced from naturally occurring pathogenic mechanisms. Use of appropriate animal controls, handled and monitored in similar manner as the experimental animals, would also be necessary to discern disease-related vs strain-related features that resemble outcomes assessed in AEG/DM studies. For example, paroxysmal patterns resembling spike-wave discharges of absence seizures or unexpected pathologies that could be epileptogenic have been reported in experimental controls as well as in wild-caught rats.[11,119]

The translation of promising preclinical AEG/DM treatments into the clinics has been a major concern, not only due to species or model differences, but also due to the significant methodological and design differences of preclinical and clinical studies and scarcity of repositories to help validate candidate targets. Efforts to address issues on reproducibility and validation of preclinical research findings but also address ethical aspects of animal experimentation have been undertaken by the joint translational initiatives of the AES and ILAE with the support of NINDS, as well as the *National Centre for the Replacement Refinement & Reduction of Animals in Research* (NC3R) that led to the ARRIVE guidelines.[6,7,21,22,57,120-124] The preclinical WG members considered as areas for future improvement the use of models that more faithfully reflect the human patient population characteristics, who are typically resistant to at least two appropriate ASMs, and creation of repositories or identification of biomarkers that could help validate and translate preclinical findings to the clinics.

Epilepsy therapy development for rare early-onset epilepsies, genetic or nongenetic, has been challenging given the obstacles and special considerations in testing new drugs in pediatric populations. These include low numbers of patient populations with rare epilepsies, different genotype-phenotype associations, and potential long-term developmental or safety concerns of treatments that could have unexpected effects upon the developing brain. This research area has therefore particularly benefitted from the development of new models for early-onset epilepsies, in rodents, zebrafish, or

TABLE 2 Opportunities and challenges for preclinical AEG/DM therapy development

	Opportunities in preclinical models	Challenges/gaps
Epilepsy types		

Known vs unknown etiology	• Etiology-relevant models enable rational, precision medicine treatments
	• Phenotypic screening or targeting common pathologies may identify treatments for epilepsies in which pathogenic mechanisms are heterogeneous, complex, or unknown
		• Induction methods may introduce bias toward specific mechanisms
		• Invasive methods of inducing or monitoring for seizures in animals may introduce confounders:
		  • Need better technologies
		• Most naturally occurring epilepsies, including unknown etiologies, cannot be modeled.
		  • Exceptions: veterinarian clients and inbred models of few epilepsy types
		  • Need more systematic studies on natural history and incidence of epilepsies in experimental animals

Generalized vs focal onset	• Many models exist
	• Many molecular-, cellular-, and network-related mechanisms or pathologies have parallels in both preclinical models and humans
	• Staging of epileptogenesis and treatment windows is more feasible than in humans
	• Across-model comparisons help dissociate the role of induction methods from epilepsy-specific pathologies
		• Gaps in knowledge on mechanisms/targets for initiation, maintenance, progression, or remission of epileptogenesis
		  • Infrastructure and strategies to identify promising therapy targets in human epilepsy populations for reverse translation
		• Challenges in validating and translating preclinical findings to the clinics
		  • Data/specimen repositories for across species validation
		  • Optimize study design and outcomes of preclinical/clinical studies to allow comparisons
		  • Biomarkers for translation and validation

Rare epilepsy syndromes and pediatric epilepsies	• Remarkable growth in genetic and nongenetic models of rare and pediatric epilepsies
	• Efficacy/tolerability treatment trials can be done using controlled and powered studies
	• Innovative experimental techniques
	• Maturational factors and other biological factors can better be studied in models
		• Numerous rare epilepsy etiologies (genetic or nongenetic) have not yet been modeled
		  • Validation of preclinical data to humans remains challenging
		  • Data/specimen repositories to allow across species comparisons
		  • Consortia and data sharing to enrich knowledge on rare epilepsies
		  • Biomarkers to translate and validate data
		  • Optimize preclinical and clinical study designs to permit comparisons and address regulatory and ethical concerns

Drug-resistant epilepsies	• Models have revealed possible mechanisms, diagnostics, and treatments for drug resistance	• Validation of preclinical data to humans is challenging • Optimize preclinical study design to model drug resistance
Strategies/study design		

Target populations	• Preclinical trials are more amenable to:
	  • Exploring targets, biomarkers, risk factors, and confounders
	  • Detect a positive drug effect by minimizing confounders
	  • Designs that can differentiate true from false successes and failures
		• Optimization of study designs is needed to:
		  • Improve translation, validation of findings
		  • Implement clinically relevant strategies
		  • Enable the identification of likely to benefit populations

(Continues)

TABLE 2 (Continued)

	Opportunities in preclinical models	Challenges/gaps

	• Studies specifically controlling for specific breeding, housing, environmental factors, genetic substrates, and/or premorbid conditions may be conducted to clarify their impact on phenotypes and drug effects
	• Across-model confirmation may reveal common pathways and evolutionarily preserved aspects of epileptogenesis
	• Infrastructure to build and disseminate expertise in creating specialized models and increase availability of animal models could be useful
		• Species-specific limitations:
		  • Breeding/housing habitat and handling are simpler and not the natural ones cannot recapitulate complex factors inherent to human everyday life conditions and stressors
		  • Source/genetic substrate affects phenotype; animal studies conducted in same strain may not extend to different strains or heterogeneous genetic substrate of human subjects enrolled in clinical trials
		  • Premorbid health condition of animal research models is not fully characterized. Premorbid factors that could influence results cannot be ascertained as in clinical studies
		  • Incidence and type of natural epilepsy and underlying pathologies unknown in models. Studies on epilepsies of unknown etiology are therefore challenging in models. Animal models of acquired epilepsies are typically induced by methods that may not fully simulate natural causes and may contribute partially to resultant phenotypes and/or pathologies
		• Access to appropriate models may not be optimal

AEG/DM strategies	• More feasible in models due to more controlled experimental conditions, flexibility to probe any stage of epilepsy development and progression, or utilize techniques not feasible yet in clinical trials	• Differences in study design, assessments and outcomes between preclinical and clinical trials may hinder translation and validation • Need to develop more clinically relevant in vivo methods to monitor and validate treatments and targets across species • Certain aspects cannot be easily modeled in animals: enrollment/compliance issues • AEG effects from *homogeneous populations* may be diluted in a heterogeneous population of people with epilepsies.
Treatments	• More flexibility to test *experimental compounds/interventions* than in the clinic, including nonconventional or experimental routes of delivery or yet untested drugs • Easier to test interventions to delineate the mechanism of AEG treatment effects for future improvements • More flexibility to monitor treatment effects on targeted mechanisms • Preclinical multicenter studies may address issues related to adequate powering of AEG/DM trials and reduce potential bias stemming from a single-center trials	• Optimization of clinically relevant methods for treatment delivery and monitoring in vivo • Tolerability and safety in humans cannot be always predicted from animal studies • Improve access to and transparency of data from treatment trials to minimize unnecessary duplications and/or facilitate repurposing of drugs • AEG/DM trials in rodents are laborious, time-consuming, and effort-consuming, making it challenging to perform dose-effect studies in powered studies from single centers, particularly in models with low epilepsy rates
Outcomes and measurements	• Seizure monitoring can be more systematic and objective in models, through the use of vEEG, rather than self-reporting • Many methods to assess for comorbidities in models with greater flexibility in incorporating in the study design	• Definition, scoring, and classification of seizures and epilepsies needs optimization • Agreement on clinically relevant outcomes and measurements, comorbidity assessment is needed

(Continues)

TABLE 2 (Continued)

	Opportunities in preclinical models	Challenges/gaps
Transparency, data sharing and reporting	• First efforts to address gaps in access to data information have been under way: • PANAChE database for ETSP screened compounds (https://panache.ninds.nih.gov/) • Registries of preclinical studies (eg, https://www.preclinicaltrials.eu) • Registries of funded preclinical AEG studies (eg, ICARE) • Publishing/reporting of data of preclinical studies (negative, replications, preliminary, etc) in journals, including open access publications • Improved capacity for big data storage and reporting and big data analyses • Development of preclinical epilepsy common data elements (CDEs)	• Collaborations are needed to share expertise and address all aspects of AEG/DM studies • Supporting AEG/DM research: • May require more effort/resources/cost/expertise than usual drug trials • Special considerations may be needed for pediatric and early-onset epilepsies

Abbreviations: AEG, antiepileptogenesis; AES, American Epilepsy Society; CDE, common data elements; DM, disease modification; ETSP, Epilepsy therapy Screening Program; ICARE, Interagency Collaborative to Advance Research in Epilepsy; ILAE, International League Against Epilepsy; PANAChE, Public Access to Neuroactive & Anticonvulsant Chemical Evaluations; PTE, posttraumatic epilepsy; vEEG, video encephalography.

patient-derived preparations, such as inducible pluripotent stem cells (iPSCs) or brain organoids that revealed new mechanisms, targets, or treatments, some of which have entered the clinical arena.[86,87,125-133] Even though animal models cannot fully predict safety or tolerability in humans,[122] they have offered insights toward potential mechanisms leading to mechanism-driven trials, that is, precision medicine trials, in small numbers of such patients. They have also revealed pathways that are critical or have changing functions during brain development,[134,135] raising caution for the implementation of treatments that influence those. Most importantly, preclinical testing has allowed rigorous testing in large numbers of homogeneous populations carrying the same genetic deficit or subjected to the same inducing method that have provided useful insights on efficacy, tolerability, or factors modifying the effects of a treatment. Animal models of rare and pediatric epilepsies have benefited with an impressive growth over the last decades and the field has started shifting from extrapolating treatments from adult epilepsy populations to preclinical treatment development in age-appropriate models of pediatric epilepsy syndromes.[87,136] Again, the development of infrastructure and biomarkers that would help translate and validate preclinical findings to humans was deemed to be important for future development.

4.2 | Strategies/study design

The value of proof-of-concept, exploratory studies for advancing knowledge on mechanisms, targets, and new treatments is well recognized. Due to the exploratory nature of these studies, the aims, study design requirements, and level of rigor and deliverables may not necessarily address all aspects expected from preclinical studies discussed here, which aim to develop and advance a treatment forward for clinical testing, that is, translational studies.

AEG/DM preclinical trials may use *target-specific* rational treatment approaches and/or phenotypic screening to monitor the effects on epilepsy or comorbidities after treatment withdrawal. Target-specific approaches provide more opportunities to stage epileptogenesis, define treatment windows, optimize and monitor treatment efficacy even at early stages, before epilepsy or comorbidities manifest, as well as to inform on whether treatment failures are due to lack of target relevance or modification or due to poor treatment efficacy. Animal models offer a better substrate to monitor these parameters, whether by terminal or by in vivo methods, which may not always be feasible in humans. *Phenotypic screening*, on the other end, is a worthy strategy when etiologies are complex or diverse, when a treatment's target is elusive or not amenable to monitoring or if effects on behaviors or outcomes that employ complex mechanisms are investigated, for example, in DMT screening trials.

The need for individualized or precision medicine approaches has been discussed for both genetic and nongenetic etiology epilepsies, considering the vast interactions and complexity of molecular, cellular, signaling, and network interactions and the age-, sex-, and timing-dependent effects of various treatments.[137-141] The preclinical WG emphasized the need to improve the infrastructure to allow precision medicine approaches for epilepsies, of both genetic and nongenetic etiologies, but also help optimize their translation into the clinics. Such infrastructure may include repositories of data and specimens to enable validation and translation of preclinical discoveries to the clinics, tools, and biomarkers to help identify target populations, deliver prognosis, and optimize treatment delivery decisions, but also research toward novel treatment delivery approaches targeting specific genes, cells, and circuits, at discreet time windows to minimize adverse effects.

Preclinical trials also enable more rigorous control of factors confounding or modifying treatment or epilepsy outcomes compared to clinical trials, by using more homogeneous populations in regards to epilepsy type, etiologies, comorbid conditions, medications or environmental factors. This may result in overestimation of the effect size for the tested treatment or in failure to replicate in clinical trials. The use of Bayesian priors based on historical control data is another approach that was recently proposed as a means of increasing statistical power of preclinical studies[142] and minimize the overestimation of effect size due to small sample sizes.[143] Across-model comparisons of a treatment effect have been proposed in the past as a means to discern treatments likely to translate. However, failure to confirm can be due to confounders that may hinder replication of a true effect, including model, species, technical, and methodological differences. Another proposed solution was the creation of multicenter preclinical trials,[22] prior to transitioning to the clinical trials, involving multiple laboratories, animals of different sources housed and bred in different settings, along the lines of clinical multicenter trials. However, the preclinical WG also acknowledged the importance of differentiating true from false failures to replicate and translate, that is, develop strategies that prevent discarding treatments that could potentially be useful in select populations. The need for in vivo clinically relevant biomarkers to help select target likely-to-benefit populations and monitor their responses to tested AEG/DM treatments was strongly emphasized as a priority in optimizing and enabling future clinical AEG/DM trials.

A key offering of the use of animals in epilepsy research has been the possibility to test a large number of experimental compounds and treatment interventions for safety and tolerability and treatment protocol optimization. For AEG/DM studies, models are superior in their flexibility to monitor target relevance and modification while investigating experimental outcomes and measurements that could not be feasible in a clinical trial, allowing for data collection that can improve the future clinical trial design. Furthermore, models offer the flexibility to test in proof-of-concept studies invasive methods for treatment delivery or monitoring that are yet difficult to implement in the clinics but could prove important if technology advances to the necessary optimization that allows their introduction to the clinical trials. Obstacles in translating include the poor or unclear correspondence of the temporal evolution of the epileptogenic process that renders translation of stage-specific treatments challenging. The availability of repositories of human specimens or databases to validate preclinical observations as well as biomarkers to help validate and translate them in vivo would be invaluable.

Aspects of clinical trials that cannot be easily addressed or modeled in animals are issues on enrollment and compliance, with perhaps an exception where veterinary clients or nonhuman primates are utilized. Monitoring medication nonadherence in a model has recently been proposed as a method to glean the effects of tested drugs from the negative and reversible effects of medication nonadherence.[144] AEG/DM trials would also benefit from inclusion of experts with diverse expertise, including, trialists, preclinical and clinical researchers, chemists or pharmacologists to optimize drug structure and formulation, pharmacokinetics/pharmacodynamic profile, experts on novel or specialized technologies useful for drug delivery and monitoring of its effect, and incorporation of various clinically relevant endpoints and measurements. A key step toward improving translation was considered to be the development of definitions and classifications for epilepsies and seizure monitoring and agreement on preferred outcome measures and endpoints for preclinical studies that would facilitate translation to the clinics.

4.3 | Transparency, data sharing, and reporting

Finally, it was recognized that sharing data on treatment effects on epilepsies or related comorbidities, whether negative or positive, would be critical for the advancement and acceleration of epilepsy treatment development. Incidental observations of various drug effects on seizures in nonepilepsy studies or preliminary data from studies that could not be completed may also be lost as they are not systematically captured. These are likely to lead to unnecessary replication of failed studies, unawareness of promising antiepilepsy effects seen in studies in which epilepsy was not the primary outcome, or to overestimation of the true effect of a drug when accessing mostly positive studies. Many journals have started accepting negative or preliminary studies for publication, and preprint servers are encouraging the open access reporting of such data. However, the majority of preclinical trials, which primarily consists of negative studies from both

TABLE 3 Preclinical working group suggestions to optimize AEG/DM therapy development

Recommendation	Description
Research initiatives	
Epilepsy brain initiative	• Development and validation of a battery of tests/tools to identify targets and circuits involved in ictogenesis, epileptogenesis or comorbidities
Novel technologies for in vivo control of therapy targets	• Development and validation of novel technologies applicable to humans that may affect targeted regulation of genes, pathways, cells, circuits in vivo
Validation and optimization of preclinical findings for clinical use	• Creation of platforms to validate and optimize preclinical discoveries for use in clinical trials for AEG, disease prevention of modification.This may include retro- or prospective studies, shared big databases and repositories for investigation and development of omics, imaging, electrophysiological or network probing tools, bioinformatics
Infrastructure	
Data sharing and big data analyses tools	• Big databases for data sharing, including published, unpublished or preliminary • Servers to host big data and tissue or sample repositories for sharing • Policies for data sharing and usage, considering intellectual properties
Workshops	
Roadmap to accelerate the advancement to clinical trials for disease prevention, modification or AEG.	• Define minimal/best preclinical dataset needed to advance to a clinical trial for disease prevention, modification or AEG for both adult and pediatric epilepsies. • Define best endpoints and predicting biomarkers for outcomes (eg, epilepsy, seizures, remission, comorbidities, consequences, drug resistance, disease progression or improvement)
Data sharing and big data analyses	Planning workshop to: • Plan for infrastructure for big databases for data sharing and optimize conditions that would enable and encourage researchers to utilize them • Identify server to house data or tissue repositories for sharing in research, including storage cataloging databases, policies for collaboration and data exchange, intellectual properties, big data analyses
Advocacy/expanding borders of epilepsy research	
Broaden epilepsy community expertise by engaging experts outside the field	• Encourage collaborations with people with expertise outside epilepsy *(immunology*, *cancer*, *bioinformatics*, *computational neuroscientists*, *network analyses*, *pharmaceutical chemists*, *genetic engineering*, *pharma*, *veterinarian research and practice*, *etc)* • Encourage creation of interoperable big databases to facilitate data exchange and processing with big databases with no epilepsy focus
Systematic utilization of medical record data	• Systematic utilization of medical record data (HIPAA compliant) to obtain insight into candidate drugs for repurposing, epilepsy comorbidities, factors influencing progression/remission, etc
Systematic probing of mechanisms through which treatments work in humans (and in animals) with epilepsies	• Systematic probing of mechanisms through which treatments work in humans (and in animals) with epilepsies

academic and pharmaceutical industry research centers, still remain unpublished. The PANACHE database (https://panache.ninds.nih.gov) is an example of an open access resource on preclinical drug testing results through the ETSP at the NINDS. A registry of preclinical studies to log preclinical trials has been created (https://www.preclinicaltrials.eu). Attempts to generate preclinical common data elements (CDEs) relevant to epilepsy studies, in hopes of helping improve the across-studies comparisons and data sharing, have provided the first sets of preclinical CDEs by the ILAE/AES Joint Translational Task Force.[21] The availability of a centralized database where investigators may find useful information on drug effects was therefore considered as a priority.

5 | OPTIMIZATION OF THE AEG/DM THERAPY DEVELOPMENT

During the preclinical WG discussions, the following initiatives were highly prioritized (Table 3). First, the WG proposed research initiatives that develop and validate (a) research tools for the identification and in vivo monitoring of targets and networks involved in ictogenesis, epileptogenesis, and comorbidities ("*epilepsy brain initiative*"), (b) technologies to achieve in vivo control and modulation of therapy targets, and (c) platforms to validate and optimize for clinical use preclinical discoveries in the sphere of AEG, DM, and disease prevention.

Second, building infrastructure to facilitate data sharing and big data analyses on epilepsy therapy preclinical studies through the creation of big databases was also considered a priority. This is also timely given the initiatives to create preclinical epilepsy CDEs, the emerging multicenter research consortia and team research groups that start utilizing such electronic databases (eg, EPIBioS4Rx, CURE Epilepsy PTE initiative, EPITARGET). Servers that can house such electronic data, repositories for specimens or resources to facilitate validation of preclinical findings, along with policies for data sharing and usage while respecting intellectual properties would be useful so as to encourage researchers to participate in this effort. A planning workshop among experts and stakeholders to create a roadmap was proposed.

Third, it was acknowledged that there is still a need to define a roadmap to accelerate the transition from preclinical to clinical trials for AEG/DM and disease prevention through organization of future workshops to (a) propose minimal and preferred preclinical datasets to advance to a clinical trial and (b) identify best preclinical endpoints and predictive biomarkers for clinically relevant outcomes.

Fourth, advocating for and expanding the borders of epilepsy research by encouraging collaborations with other research areas, systematic utilization of medical record data, in a HIPAA (health insurance portability and accountability act) compliant manner and research data to allow identification of drug candidates for repurposing, probe candidate mechanisms through which treatments work in epilepsy, or reveal risks or protective factors for epilepsies and their comorbidities.

6 | CONCLUSIONS

Despite the significant progress in epilepsy research and therapeutics, there is an urgent need to identify treatments that prevent or reverse the development of epilepsy. Following the 2010 NINDS-sponsored antiepileptogenesis workshop, several collaborative epilepsy research programs and translational initiatives have been created to promote AEG/DM research studies. At the 2018 AEG workshop, the preclinical WG recognized several opportunities to advance the field forward, including the diversity of animal models, new tools to probe targets and biomarkers, and increasing knowledge about the mechanisms underlying epileptogenesis and comorbidities. A significant gap is the difficulty in translating and validating preclinical discoveries to the clinic as well as the need to de-risk AEG/DM research. Looking forward, the WG proposed as high priority areas of research the development and validation of clinically relevant tools to identify, monitor, and regulate in vivo targets, processes, and networks involved in ictogenesis, epileptogenesis, and comorbidities, as well as develop infrastructure and strategies to validate and translate preclinical findings into the clinic. The engagement of the broader research community, as well as of other stakeholders, including expert patients, caregivers, or consumer organizations, into refining of research strategies and tools, data and expertise sharing, and enabling big data analyses was deemed essential in these efforts.

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CONFLICT OF INTEREST

AS Galanopoulou is Editor-in-Chief of *Epilepsia Open* and has received royalties for publications from Medlink, Elsevier and Morgan & Claypool publishers but has no conflict of interest for the contents of this report. R Twyman is CEO and founder of Amron Neuroscience but has no conflict of interest for the contents of this report. KS Wilcox serves on the Scientific Advisory Board of Mend Neuroscience and Blackfynn, Inc, and is a consultant for Xenon Pharmaceuticals but has no conflict of interest for the contents of this report. None of the other coauthors declare conflicts of interest. This report does not represent the official view of the National Institute of Neurological Disorders and Stroke (NINDS), the National Institutes of Health (NIH), or any part of the US Federal Government. No official support or endorsement of this article by the NINDS or NIH is intended or should be inferred. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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