A Novel Translational Concordance Framework Identifies Preclinical Seizure Models with Highest Predictive Validity in Focal and Generalized Epilepsies

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Background

- Epilepsy is a prevalent, complex disease characterized by unprovoked spontaneous seizures.
- Almost a third of epilepsy patients are refractory to conventional antiseizure medications (ASMs), highlighting the urgent need for new treatments.
- Central to the development of novel treatments is testing of anticonvulsant activity in preclinical epilepsy and seizure models.
- While various well-established acute and chronic models exist, the predictive validity of each model across the wide spectrum of epilepsies is less clear.

➢ *Here, we sought to establish the concordance between commonly used preclinical models for the clinical epilepsy spectrum spanning focal and generalized epilepsies to define model(s) with the highest predictive validity, and thus broadest utility, for novel ASM drug development efforts.*

Methods

Praxis Analysis of Concordance (PAC) framework

- The Praxis Analysis of Concordance (PAC) framework was implemented to assess the translational concordance between *preclinical* and *clinical ASM response* across the clinical epilepsy spectrum for 32 FDA-approved ASMs that are available in the United States.
- *Preclinical ASM responses* in seizure models that have been used historically and that have been established by the Epilepsy Therapy Screening Program (ETSP) were collected from searches performed in PubMed and the ETSP PANAChE database.
- *Clinical ASM responses* were collected based on searches performed in PubMed, American Epilepsy Society, Epilepsy Foundation and National Institute for Health Care and Excellence websites.

Preclinical and Clinical ASM Response

- Protective indices (PI) based on reported TD_{50} and ED_{50} values were calculated for each ASM in each preclinical model. A weighted scale representing relative anticonvulsant effect was then used to grade the *preclinical ASM responses* for each seizure model ranging from potent anticonvulsant (PI > 10) to proconvulsant.
- Published reports of ASM use in patients with focal and generalized epilepsies were similarly evaluated and a weighted scale representing prescribing patterns was used to grade the *clinical ASM responses* for each indication ranging from common monotherapy to contraindicated.

Translational Concordance Scoring

- In order to assess and compare the predictive validity of preclinical models, a unified scoring matrix was developed to assign a translational score that captured the spectrum of complete discordance (-1) to complete concordance (1) between *preclinical* and *clinical ASM responses* for each preclinical model and clinical indication combination.
- Scores were then summed and normalized to generate a *global translational concordance score.*

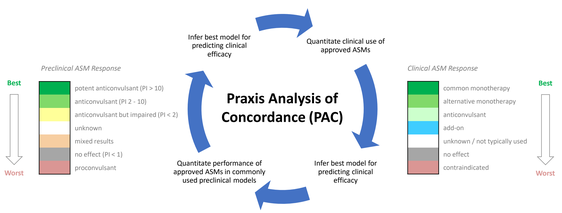
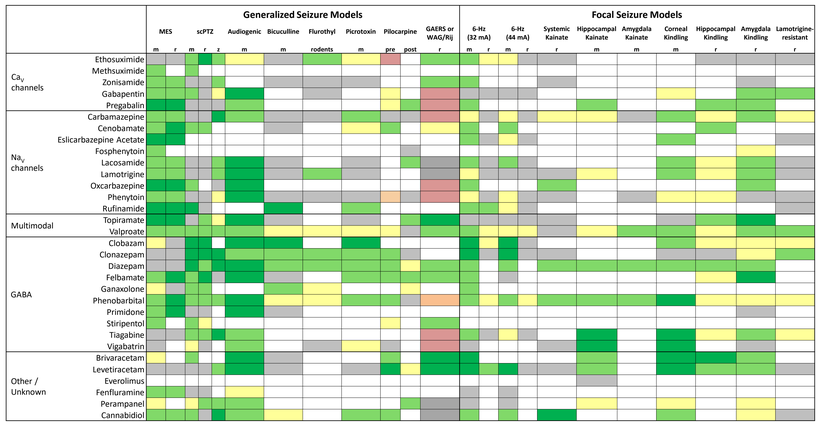


Figure 1. PAC Analysis Framework. An overview of the PAC analysis framework. Performance of approved ASMs in commonly used preclinical models was evaluated based on reported TD_{50} and ED_{50} values, with *preclinical ASM response* for each model graded according to a weighted scale. Clinical use of approved ASMs was similarly evaluated based on established reports, with *clinical ASM response* for each indication graded according to a weighted scale.

Assessing Translational Concordance Between Preclinical and Clinical Responses Across the Epilepsy Spectrum Identifies Preclinical Models with Highest Predictive Validity

Preclinical ASM Response

- Sodium channel blockers tend to perform best in maximal electroshock seizure (MES), have mixed effects in subcutaneous pentylenetetrazole (scPTZ) and are less efficacious (or efficacious at impairing doses) in 6-Hz.
- GABAergics and modulators of SV2A (synaptic vesicle protein 2A) tend to perform best in 6-Hz, with less efficacy in MES.
- Most ASMs show efficacy in the audiogenic seizure model, with a wide range of PI values.



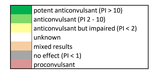


Figure 2. Preclinical ASM Response. The preclinical efficacy of 32 FDA-approved ASMs currently available in the US was examined in a total of 23 seizure models across multiple species. Preclinical seizure models were grouped according to the type of seizure induced in the model (generalized or focal). ASMs were grouped according to class/target, and captured calcium and sodium channel blockers, multimodal agents, GABAergic agents as well as agents with other mechanisms of action (including mTOR inhibitors, modulators of SV2A, selective serotonin reuptake inhibitors, and AMPA inhibitors). Colors denote grading of *preclinical ASM response* based on reported TD_{50} and ED_{50} values for each model, resulting in a weighted scale capturing relative preclinical anticonvulsant potential. m=mouse; r=rat; pre=before pilocarpine-induced *status epilepticus* (preventative); post=after pilocarpine-induced *status epilepticus* (interventional).

Clinical ASM Response

- Use patterns tend to vary by indication across the generalized epilepsies.
- Common monotherapies for focal onset seizures include sodium channel blockers, valproate and SV2As (**Fig. 3**).

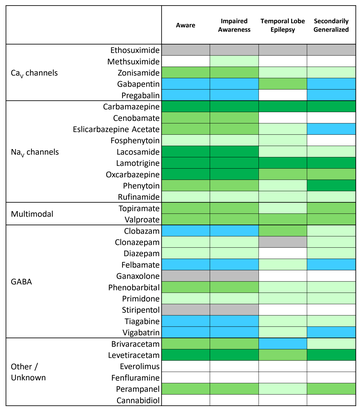


Figure 3. Clinical ASM Response in Focal Epilepsies. Clinical use of the same 32 FDA-approved ASMs was evaluated based on established reports. Colors denote grading of *clinical ASM response* based on prescribing patterns for each indication, resulting in a weighted scale capturing relative clinical anticonvulsant potential.

Calculation of Translational Concordance

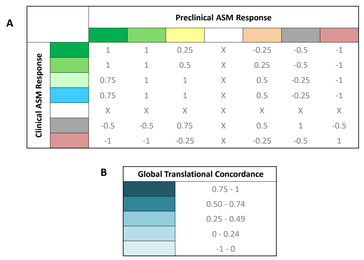


Figure 4. Translational Concordance Scoring. **A)** A unified scoring matrix was developed to assign translational concordance between *preclinical* and *clinical ASM response.* Values ranged from 1 for complete concordance to -1 for complete discordance. **B)** For each preclinical seizure model and clinical indication combination, individual ASM concordance scores were first calculated, then summed and normalized (total translational concordance score/ total number of ASMs with data available) to generate a global translational concordance score, weighted from highest (0.75 to 1) to lowest (-1 to 0) concordance.

Mouse MES, Audiogenic and 6-Hz 32 mA Models Offer Greatest Versatility for ASM Drug Discovery

- Preclinical models with greatest concordance for generalized epilepsies were:
  - GAERS and WAG/Rij models for absence, myoclonic and atonic seizure types
  - MES (mouse and rat), audiogenic, zebrafish PTZ, pilocarpine (preventative), mouse 6-Hz (32 mA) hippocampal kainate and corneal, hippocampal and amygdala kindling models for *status epilepticus* and tonic-clonic seizures
- Across the focal epilepsies clinically, the preclinical models that had the highest concordance were audiogenic, hippocampal kainate, corneal kindling, MES (mouse and rat), zebrafish PTZ, pilocarpine (preventative), mouse 6-Hz (32 mA), and hippocampal and amygdala kindling (**Fig. 5**).
  - The list condenses to four main models (audiogenic, MES, mouse 6-Hz (32 mA) and amygdala kindling) following exclusion of models with limited data – defined as less than two-thirds of ASMs tested**.**

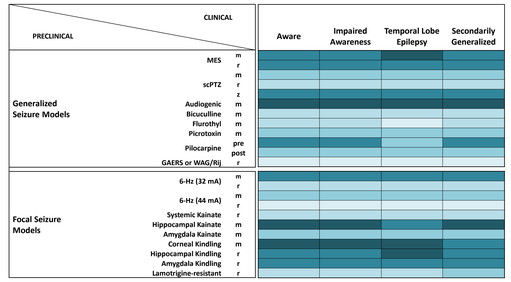
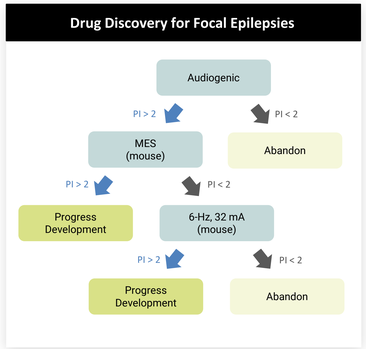


Figure 5. Translational Concordance for Focal Epilepsies.

Across all focal epilepsy types, the PAC Framework identifies mouse MES, audiogenic and 6-Hz 32 mA as models with greatest predictive validity and versatility for ASM drug discovery.

Conclusions

- **Using a newly developed scoring matrix to assess translational concordance and predictability, this study provides novel insights into the clinical validity of commonly used preclinical seizure models across the clinical epilepsy spectrum.**
- **Notably, we highlight mouse MES, mouse audiogenic and mouse 6-Hz (32mA) as three acute seizure models consistently demonstrating the highest predictive validity, irrespective of clinical indication.**
- **Based on these findings, we provide a pragmatic approach with decision tree (*right*) to support efficient use of resources and in consideration of the 3Rs of animal ethics for novel ASM development for focal epilepsies.**



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