

The NINDS Epilepsy Therapy Screening Program:

A report of the NINDS Epilepsy Therapy Screening Program Working Group, of the National Advisory Neurological Disorders and Stroke (NANDS) Council

May 27, 2020

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Introduction and Overview:

The National Institute of Neurological Disorders and Stroke (NINDS) established the Anticonvulsant Screening Program (ASP) in 1975 and changed its name to the Epilepsy Therapy Screening Program (ETSP) in 2016. The original ASP responded to a critical need for new anti-seizure medications and for promoting industry interest in their development. The name change to ETSP reflected a refocusing of the program's priorities to address unmet needs in epilepsy, including drug refractory epilepsy, epileptogenesis, and disease modification. Since its inception, the program has contributed to bringing eleven drugs to market for epilepsy, with a major role in some and a minor role in others. Most recently, SK Life Science acknowledged the important role of the ETSP in the preclinical identification of the antiseizure activity of XCOPRI (cenobamate), which the FDA approved in November 2019 for the treatment of partial onset seizures in adults.

Although many details of the program have changed over the years, the basic paradigm has remained the same. Researchers from academia and industry, in the United States and abroad, submit compounds for testing in the program, for which there is no charge to participants. The program rigorously tests compounds that meet the entry criteria in a series of standardized rodent seizure models through a contract site. The testing flow is adjusted based on prior knowledge of the compounds and results of early tests. NINDS program staff report the results of the testing back to the researchers and provide advice on further drug development steps. The program strictly preserves participants' confidentiality and intellectual property.

The ETSP also maintains a database of chemical structures and test results that provides insights on structure-activity relationships. In 2014, NINDS launched the Public Access to Neuroactive & Anticonvulsant Chemical Evaluations (PANACHe <https://panache.ninds.nih.gov/>) web based resource. PANACHe contains public and non-confidential chemical structures and biological data for compounds that have been screened through the program, including reference compounds.

In 2015, NINDS established the ETSP External Consulting Board (ECB). The ECB meets, whether in person or virtually, every three to four months. The five current members of the ECB have deep expertise from academia and industry that collectively spans basic and clinical epilepsy research, epilepsy clinical practice, and research and development of epilepsy drugs. The ECB members individually provide their advice on many aspects of ETSP function, including model selection, screening flows, monitoring progress, and overall strategy.

Contract history, costs, and earlier reviews:

NINDS awarded the initial contract for ETSP (then ASP) model development and screening to the University of Utah in 1974 through an open competition. Since then, the program has been continuously supported through contracts to the University of Utah, via open competitions in 1980 and 1984, and then renewed on a sole source basis until 2016, when the contract was again awarded to the University of Utah through an open competition. The principal investigator of the current contract is Karen Wilcox, Ph.D., and the average annual funding for FY2016-2019 was \$3.7 million. Currently, five NINDS staff members work on the ETSP, representing

approximately three full time equivalents (FTEs), given staff members' other non-ETSP responsibilities. The total cost of the ETSP program in FY2019, including the NINDS contract to the University of Utah, estimated NINDS personnel costs, and additional NINDS internal contract costs was \$4.5 million.

External groups reviewed the ASP in 1982, 1987, and 1992. Following a twenty-year gap in reviews, two successive working groups of the National Advisory Neurological Disorders and Stroke (NANDS) Council, prior to the current NANDS Working Group, reviewed the ASP program and reported to Council in 2012 and in 2015.

In a following section, this report discusses progress on and proposed updates to each of the recommendations of the 2015 NANDS Working Group report. The recommendations from the 2012 report had a major impact on improving the ASP and are noted briefly here. The 2015 report found that NINDS had, as recommended in 2012, made substantial improvements to program leadership, operating procedures and quality control, and transparency and communication, both within NINDS and between NINDS and ASP contract staff. The 2015 report strongly endorsed the earlier report's recommendation to shift ASP priorities from identification of undifferentiated acute seizure drugs toward advancing potential drugs for drug refractory epilepsy, epileptogenesis, and disease modification. The 2015 group was encouraged that the program had adopted new rodent models for drug refractory epilepsy into the screening flow and had begun to explore other models for drug refractory epilepsy, epileptogenesis, and disease modification. However, the 2015 report emphasized that the shift had not yet gone far enough.

In response to the 2012 recommendation to improve integration with other NINDS programs, the ETSP has established productive interactions with NINDS basic, translational, and clinical scientific program staff in general, and a few specific program activities are worth noting. From FY2007-2017, the NIH Office of the Director funded a second screening track through the ETSP as part of the NINDS led trans-NIH Countermeasures Against Chemical Threats (CounterACT) program. In FY2019, the NIH Helping to End Addiction Long-term (HEAL) initiative provided a one-time \$2.6 million supplement to the ETSP contract to support launch of a new NINDS-led preclinical screening program for non-addictive pain drugs, modeled explicitly on the ETSP. The HEAL Initiative has recently launched that program, the Preclinical Screening Platform for Pain (PSPP) (<https://www.ninds.nih.gov/Current-Research/Trans-Agency-Activities/NINDS-Role-HEAL-Initiative-PSPP>). ETSP participants are also transitioning to support through other programs led by the NINDS Division of Translational Research, including, for example, a project in its fourth year of the milestone-driven Blueprint Neurotherapeutics Program to develop new treatments for KCNQ encephalopathies.

2020 NANDS Working Group:

The 2020 NINDS Epilepsy Therapy Screening Program Working Group of the National Advisory Neurological Disorders and Stroke (NANDS) Council includes all five members of the ECB and two additional members. Collectively, the working group provides expertise in basic and clinical epilepsy research, epilepsy clinical practice, and research and development of epilepsy drugs. The Working Group includes members who are familiar with the program,

including service on past reviews and on the ECB, as well as those who are new to the program, and the group represents perspectives from academia, industry, and non-governmental organizations. Two current members and one former Council member are on the working group. The roster of the group is appended to the charge, which is included in the appendix to this document.

In December 2019, the NINDS Director charged the Working Group. At that meeting, the ETSP staff also presented and discussed with the Working Group what information they required to carry out their charge. The Working Group received this information in February 2020, with supplemental information provided in March. The Working Group met virtually in March 2020, rather than in person, due to public health circumstances. Following extensive discussions with the NINDS ETSP and Utah contract site staff at the March meeting, the working group developed their recommendations through electronic communications.

Findings and Recommendations:

As called for in the Charge to the working group, the Working Group first reviewed the extent to which the ETSP program had addressed the recommendations from the 2015 NINDS ETSP Working Group report, whether each recommendation is still relevant or should be modified, and what still needs to be done. Following discussion of those findings, this report then presents priorities and additional recommendations from the 2020 Working Group. The overall findings of the Working Group are that the ETSP program continues to make important contributions to progress in epilepsy therapy, and the NINDS and Utah contract ETSP staff have been very responsive in implementing previous recommendations of the review groups and of the ECB members on quality control, screening processes, transparency, and rigor.

Progress on and Updates to 2015 Working Group Recommendations:

2015 Recommendation I. Establish an Advisory Board or similar group for the program, whose members can provide advice on an ongoing basis.

The NINDS established the External Consulting Board (ECB), which has met regularly since 2015, and the ETSP has been very responsive to the suggestions of the individual ECB members. The 2020 Working Group offered suggestions on improving the value of the ECB, which should certainly continue. The ETSP should explore having fewer but longer meetings of the ECB (perhaps two in person meetings per year). The ETSP should also provide agenda topics and information to be discussed at the meetings with sufficient advance time to enable ECB members time to prepare (perhaps a week or two). The ECB meetings should also set aside time and provide analyses to support strategic level discussions in addition to the valuable consideration of details of models and testing. Analyses of how the distribution of presumed targets of tested compounds has evolved (or not) over time provides one example of an analysis to frame a strategic discussion and inform potential outreach for drugs with novel mechanisms. Adding a lay member to the ECB would provide an additional perspective that would be particularly valuable for strategic discussions and outreach.

2015 Recommendation II. Accelerate the shift in emphasis toward treatments for drug refractory epilepsy, epileptogenesis, and disease modification... An early step will be to develop a new name for the program.

The Anticonvulsant Screening Program (ASP) changed its name to the Epilepsy Therapy Screening Program (ETSP) in 2016, reflecting the shift in emphasis. The 2020 Working Group strongly agrees that the recommended shift in emphasis is still valid and crucial to address the unmet needs of people with epilepsy.

The Working Group noted that the ETSP has implemented new models and a revised testing flow to address drug refractory epilepsy, as recommended. The program cannot validate those models until there are drugs that work for people with drug refractory epilepsy. Validating these models against successful drugs as they emerge will be a priority going forward, with some drugs now emerging that show promise.

Although the ETSP has taken steps toward tackling epileptogenesis and disease modification, with additional models under development, the program has shown less progress in tackling these unmet needs, which are more difficult problems. The Working Group will discuss this further in the future recommendations section below.

2015 Recommendation III. Align screening with specific goals for different types of treatments (drug refractory epilepsy, epileptogenesis, and disease modification).

A. For drug refractory epilepsy, further streamline the current standard screening flow into only two levels (“Identification” and “Differentiation”) with two associated go/no go decisions by removing redundant assays and reordering others so that less promising compounds for drug refractory epilepsy can be ruled out earlier in the process.

The ETSP has streamlined the standard screening flow into “Identification” and “Differentiation” levels as recommended, and the program has removed multiple redundant assays, thus enabling the testing to significantly improve efficiency in ruling out less promising compounds. The Working Group recommends that the ETSP continue to discuss with the ECB further opportunities to remove redundant models from the testing flow, for example, whether the 6 Hz model is sufficiently predictive to reduce or eliminate the use of the maximal electroshock (MES) model, and thus further improve efficiency and reduce unnecessary use of animals.

B. For epileptogenesis and disease modification, clinically validated models are also lacking, and while some models are already being pursued by the program, further effort should be made to deliberately consider others, as described above, with input from external experts and the epilepsy research community.

The ETSP has begun to address epileptogenesis and disease modification, e.g. by using the rat rendered chronically epileptic by prior exposure to status epilepticus-inducing doses of i.p. kainate, performed by the University of Washington subcontract site, as well as with introduction of the Theiler’s Murine Encephalitis Virus (TMEV) model and with other models, including Dravet models and an intra-amygdala kainate model, currently under development. However, as

noted above, there has been less progress in developing screening for drugs for epileptogenesis and disease modification compared with models for drug refractory epilepsy. This will be discussed further in the priorities and new recommendations section below.

2015 Recommendation IV. Revise the program’s approach to assessing the impact of compounds on comorbid conditions beyond seizures, including cognitive impairment and psychiatric conditions such as anxiety and depression.

As the 2015 Working Group noted, comorbid conditions beyond seizures continue to have a major impact on quality of life for people with epilepsy, but the early stage screening assays then in use by the ETSP had limited predictive value, and testing for effects on comorbid conditions is more appropriate as part of late stage characterization of drug candidates. In keeping with this recommendation, the ETSP has halted routine use of the cognition comorbidity assays, which included the mouse novel object recognition test, the long-term potentiation rat brain slice model, and the Morris Water Maze test. The ETSP is using the Irwin Test to evaluate the qualitative effects of compounds on behavior and physiological function. This test observes drug effects on exploratory behaviors, gait, startle reflex, grip strength, pain response, pinnae reflex, corneal reflex, righting reflex, and visual placement. It is a well-recognized battery that serves to identify early in testing potential adverse effects of drug candidates on behavior, which is appropriate.

2015 Recommendation V. Look beyond the traditional role of the program to facilitate and drive advances,

A. Profile tool compounds to develop a “reference library” that relates activity against a particular target to activity in the program’s core models of refractory epilepsy, and then ultimately in models identified as important for a given disease modification objective.

The ETSP has made good progress on this recommendation, with several publications. Looking forward, it will be especially helpful to the epilepsy community to systematically consolidate the results in an easily accessible manner that enables comparison of results in animal models with the experience in human patients. Understanding how results on specific testing models may predict clinical usefulness for specific epilepsy conditions or patient populations will contribute toward the broader goal of rational choice of epilepsy treatment for patients.

B. Prioritize and self-nominate compounds and targets for testing, with input from the epilepsy research community and external program consultants.

This recommendation has not been specifically addressed, although the ETSP has tested reference compounds and is making data available through PANACHÉ. Some further recommendations relevant to this idea are presented below in the 2020 Working Group’s priorities and recommendations section.

2015 Recommendation VI. Take further steps to ensure efficacy data are not confounded by ADME-tox issues.

The ETSP program now requires potential participants to provide any supporting ADME-tox data and to indicate whether they can provide PK support during the course of the ETSP testing. The contractor has discovery level PK support that has been used on a very limited basis. The 2020 Working Group will further discuss this issue in the priorities section of this report.

2015 Recommendation VII. Hold an open competition for the next period of support for the program.

The NINDS held an open competition for the current ETSP contract as recommended. The NINDS released the Request for Proposals in March 2016, which closed in May 2016. A Special Emphasis Panel (SEP) reviewed the proposals, and NINDS awarded the contract on September 30, 2016 to the University of Utah (Karen Wilcox, Ph.D., Principal Investigator). The final contract included two subcontractors, SynapCell, Inc., France (Dr. Corrine Ricaurde, Principal Investigator) to perform the intrahippocampal kainate mouse model of temporal lobe epilepsy, and the University of Washington (Dr. Steve White, Principal Investigator), to perform a rat model of epileptogenesis and disease modification, as well as selected rigor and replication testing to compare results with the Utah site (which has been done, with encouraging results).

Priorities and Additional Recommendations of the 2020 Working Group:

As noted in the previous section of this report, the Working Group regards testing for drug refractory epilepsy as a continuing priority for the ETSP. The group also proposed several updates to previous recommendations, including for example, ways to improve the usefulness of the ECB and the value of further consolidating information from the accumulated legacy of testing in a more accessible form. Although the Working Group considered several potentially fruitful avenues to extend the activities of the ETSP, the strategic imperative for progress in preventing epileptogenesis and in disease modification, and the challenges that presents, dictates that the program maintain a sharp focus on that goal. Toward that end, the following complementary, and equally important, future priorities emerged from the discussion.

Enhance the early consideration of ADME issues in the screening process. As the 2015 NINDS Working Group noted, limited data on PK/ADME could lead to false negatives or false positives. Lack of adequate data on how effectively a candidate compound reaches the presumed targets in the brain becomes even more critical as screening becomes more reliant upon chronic dosing, given the longer monitoring time and greater resources that it requires. Although limiting screening to compounds for which participants can provide adequate ADME data can improve the efficiency of the program, that limitation might preclude testing of promising compounds from academic or small business investigators who have fewer resources. The NINDS should explore whether providing ADME testing can efficiently be done via the ETSP contract or by leveraging other NINDS or NIH resources. The costs of providing ADME services to a limited subset of participants may be offset by the greater efficiencies in the testing flow that the program has already implemented by eliminating redundant or minimally informative tests.

The development and implementation of epileptogenesis and disease modification testing models that can more rapidly translate to humans, including those that use biomarkers, is a high priority. The development of reliable and valid models of epileptogenesis and disease

modification has been very challenging, not in the least because only a small percentage of animals develop epilepsy in the available trauma, infection, or inflammation induced epilepsy models, and even those animals that do develop epilepsy may have infrequent seizures. Given the enormous challenges, the ETSP should focus on optimizing the viral and intra-amygdala kainic acid models that have already been introduced, with enhanced attention to the identification of biomarkers that might predict which subset of animals are most likely to develop epilepsy. Notably, biomarkers may not only improve the feasibility of models for testing, but also be useful in transitioning potential drug candidates to the clinic.

That said, the Working Group discussed the possibility of including additional models of epileptogenesis, focusing on traumatic brain injury (TBI) in particular. Several ideas emerged from this discussion. Whether common mechanisms underlie epileptogenesis caused by status epilepticus and TBI is presently unclear. Understanding the molecular mechanisms of epileptogenesis following TBI would provide targets for developing anti-epileptogenic drugs and a focused assessment of efficacy of such drugs in animal models. Although it is debatable whether TBI models suitable for the screening program currently exist, intensive efforts centered on epileptogenesis caused by TBI funded by NINDS, the Department of Defense, and others are currently underway, strengthening the likelihood of progress in this area. The Working Group recommended that progress in this area be carefully monitored and discussions of the ideas outlined above be included in future meetings between the ECB and ETSP. In the meantime, investigation of additional models should not dilute the focus on the current models which would diminish the chances of success.

The ETSP should encourage testing of non-small molecule therapies, to the extent that this can be accomplished within the existing testing models. Although the ETSP does test non-small molecule drugs, inclusion of these agents should be further encouraged and better advertised. Over the last several years, several other promising modalities have emerged, including, for example, anti-sense oligonucleotides and RNAi. To the extent that the ETSP can accommodate non-small molecule agents without major investment of time and resources to modify the current testing protocols, there is considerable potential for finding agents with novel mechanisms of action.

Other recommendations:

The Working Group discussed other possible changes or additions to the ETSP, which may be useful but should not detract from the focus on the major priorities described above.

Genetic models: Research on genetic causes of epilepsy has advanced rapidly over the last several years. However, the Working Group did not recommend that the ETSP dilute its current priorities by increasing its focus on mouse genetic models, nor expand into zebrafish or cell models. Choosing among the many emerging genetic models and the complexity of genetic influences are obstacles to taking on additional genetic models. Not only are there hundreds of genes implicated in the epilepsies, but different mutations in a single gene can have different consequences, as can the same mutation on different genetic backgrounds. The Working Group did suggest, however, that the NINDS should explore leveraging the ETSP to serve as an informational hub that could connect researchers in academic and industry drug development programs with academic investigators who have expertise in particular genetic models. Testing drug candidates in additional models could be attractive in augmenting the informational packages for moving a drug forward in development and approval. Although the Working Group does not recommend expanding the testing to additional genetic models, the effort invested in development of the Dravet model for ETSP screening has been valuable, and the Dravet model should be continued.

NINDS should proactively explore and conduct outreach to bring in drugs with novel mechanisms and targets. The ETSP should also engage NINDS staff broadly, and outside experts as appropriate, to proactively explore novel mechanisms and potential targets for anti-epileptogenic and disease modifying drugs. The ETSP should then conduct outreach to bring novel candidates that target those mechanisms into ETSP testing. The emerging publications from the NINDS 2018 “Accelerating the Development of Therapies for Anti-epileptogenesis and Disease Modification Workshop” (<https://meetings.ninds.nih.gov/assets/2018AEDMWorkshop/UpdatedAgenda.pdf>) will inform these discussions, as will the NINDS Center without Walls “Epilepsy Bioinformatics Study for Antiepileptogenic Therapy” ([EpiBiosS4Rx](#)) and the 2020 update of the NINDS/AES Epilepsy Research Benchmarks and Key Priority areas.

Surveying participants and potential participants: The Working Group suggested that NINDS survey participants in the ETSP on their satisfaction with and suggestions for improving the program. Sending this survey to investigators who inquire about participating in the program, but do not ultimately do so, would also be informative.

Conclusion:

The ETSP is an important component of NINDS programs to address the unmet needs of people with epilepsy, including drug refractory epilepsy, anti-epileptogenesis, and disease modification. Although addressing these needs is challenging, the NINDS ETSP and the Utah contract staff have shown a strong commitment and responsiveness to recommendations, and the program has shown impressive improvements and progress. The 2020 NINDS Working Group strongly supports continued investment in this important program.

National Advisory Neurological Disorders and Stroke Council Working Group on the NINDS Epilepsy Therapy Screening Program, 2020

Charge and Roster, November 2019

Background:

The National Institute of Neurological Disorders and Stroke (NINDS) established the Anticonvulsant Screening Program (ASP) in 1975 to screen compounds submitted by academic and industry investigators from the United States and abroad for antiseizure potential in several standardized animal seizure models, while protecting confidentiality and intellectual property rights. The ASP has contributed, in a major or minor way, to bringing ten antiseizure drugs to market.

In 2011, a working group of the National Advisory Neurological Disorders and Stroke (NANDS) Council, with added outside expertise, recommended several changes to the ASP operations, including management and quality control improvements. The working group also emphasized that NINDS should shift the focus of the program to meet the most urgent unmet needs for epilepsy treatment and prevention--therapies for pharmacoresistant epilepsies, epileptogenesis, disease modification, co-morbidities of epilepsy, and targeted treatments for specific epilepsy subtypes.

A 2015 working group of the NANDS Council found that the program had made substantial progress in implementing the 2011 recommendations at the operational level, with improvements in efficiency, communication, transparency, and quality control. The 2015 group strongly agreed with the prior recommendations for changes in program priorities but noted that the program needed to go further in implementing those changes. Because clinically validated animal models and a proven path forward are not yet apparent for the new priorities, the working group suggested that the program look beyond its traditional mode of operation and structure to meet the current priorities for epilepsy therapy.

Among several actions in response to the 2015 external working group report and the subsequent Council discussion, NINDS changed the ASP name to Epilepsy Therapy Screening Program (ETSP) in 2016. This reflected the importance of shifting the focus of the program toward treatments for pharmacoresistant epilepsy, anti-epileptogenesis, and disease modification. NINDS also established the ETSP External Consultant Board (ECB) to address the call for the Institute to engage the advice of external consultants and link to the epilepsy community on an ongoing basis to guide the program. The ETSP also addressed several specific recommended changes in the testing protocol. NINDS held an open competition, as recommended, for a new ETSP contract, which was awarded in September 2016 and addressed several elements from the 2015 report in the Statement of Work.

Purpose of the working group:

The overarching purpose of the 2019/20 working group is to assess how the ETSP can best advance epilepsy therapy development, considering the current needs of people with epilepsy, the state of the science, and the unique position of the NINDS within the drug development landscape. The working group may, for example:

- Review progress on the 2015 report recommendations
- Examine and provide feedback on the suitability of the current ETSP procedures and screening workflows, animal models, agents tested, data sharing, outreach to investigators, budget, personnel, contract and subcontract sites and output, etc.
- Identify what ETSP priorities should be going forward, including:
 - current activities that should be maintained
 - current activities that should be deemphasized
 - new or promising activities that should be emphasized.
- Provide perspective on how the ETSP program can better integrate with the current public and private sector therapeutic development environment.

Working group composition:

The working group will include nine members, all from outside the NIH: two members from the current NANDS Council, all current members of the ETSP External Consultants Board, and two additional members. The collective experience brings expertise in adult and pediatric epilepsy, in epilepsy drug development and drug development generally, from academia and industry, and in the interests of the epilepsy non-profit community. A roster of members and their relevant affiliations is appended to this document.

Working group activities and deliverables:

- The working group will work closely with NINDS staff to identify data, analyses, or background materials that will help the group formulate its recommendations. NINDS staff will serve as liaison to the ETSP staff and to the contract facility staff who will provide this supporting information.
- The group will hold teleconferences to orient the new members, have the first teleconference with the full working group in conjunction with the regularly scheduled ECB meeting on December 2nd, and will hold an in person working group meeting at NIH, tentatively scheduled for March 11th. NINDS will facilitate further calls prior to or after the in-person meeting as requested by the group.
- The group may discuss and deliberate among themselves via conference calls, emails, or other means as they deem appropriate, with or without NINDS staff participation. The group may also conduct virtual or in person meetings with NINDS or ETSP site staff as the group determines appropriate.
- The group shall submit summaries or minutes of all meetings to be filed with the NANDS Council.
- The final product of the report will be a written summary report and a final set of recommendations to be presented to the NANDS Council for deliberation in open session during the May 27th 2020 Council meeting.

Roster:

Chair: Amy Brooks-Kayal, MD, Chair in Pediatric Neurology, Professor of Pediatrics, Neurology & Pharm. Sciences, University of Colorado School of Medicine, Children's Hospital Colorado

Donna L. Hammond, Ph.D., Vice Chair for Research, Director, PREP@Iowa, Professor of Anesthesia and Pharmacology, University of Iowa

Jennifer A. Kearney, Ph.D., Assoc. Prof of Pharmacology, Northwestern University

Henrik Klitgaard, Ph.D., Consultant, UCB Biopharma SPRL

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James McNamara Sr, M.D, Professor, Department of Neurobiology, Duke University

*Eileen M. Murray, MM, CAE, Executive Director, American Epilepsy Society

*Steven L. Roberds, Ph.D., Chief Scientific Officer, Tuberous Sclerosis Alliance

Steven D. Young, Ph.D., Consultant, Steven Young Consulting

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