NINDS Anticonvulsant Screening Program (ASP) working group report and update

History and overview

- Established in 1975
- Researchers from academia and industry submit compounds for screening in series of rodent seizure models (second track added in 2007 for chemical nerve agent countermeasures)
- Screens directed by NINDS staff, performed at contract facility (University of Utah)
- NINDS staff report results to participants, advise on future development
- ~ 30,000 compounds screened to date
- Major/minor roles in 9 marketed antiepileptic drugs (AEDs) since 1990
NINDS Anticonvulsant Screening Program (ASP) working group report and update

The ASP Working Group

- Considered ASP’s value to epilepsy research and drug development within the current scientific and pharmaceutical landscape
- Made recommendations for future of the program (focus, strategies, and configuration)
- Presented final report on February 16, 2012

Robert E. Pacifici, PhD, Chair
CHDI Management/CHDI Foundation

Susan Axelrod
Citizens United for Research in Epilepsy

Amy Brooks-Kayal, MD
Children's Hospital Colorado

Henrik Klitgaard, PhD
UCB Pharma

James McNamara, MD
Duke University

Jeffrey L. Noebels, MD, PhD
Baylor College of Medicine

Roy Twyman, MD
Johnson and Johnson
Working group findings

Many drugs now available to stop seizures, and the ASP has facilitated the development of a number of the new AEDs.

However
- Treatments fail to achieve seizure control in \(\sim\) 1/3 with epilepsy
- No treatments modify disease course or prevent its development
- Efficacious treatments may suffer from poor side-effect profiles

Therefore, the ASP should
- shift its focus to address most critical unmet needs
- adapt to a drug development landscape that has evolved
NINDS Anticonvulsant Screening Program (ASP) working group report and update

**Selected working group recommendations**

- Revise the mission of the ASP to focus on:
  - Disease modification (epileptogenesis; disease course)
  - Pharmacoresistant epilepsies
  - True comorbidities of epilepsy
  - Targeted and optimized interventions

- Reshape the ASP as a translational program and integral component of NINDS epilepsy research.

- Refine operating procedures to maximize quality of compounds tested and allow rational decision making.

- Determine and implement a process for selecting or developing new models for incorporation into the ASP.
Implementation update: recent changes and plans

- Revised requirements for entry into the program
  - rationale for screening as potential AED
  - additional information requested when available (in vitro and in vivo data, PK/ADME, stability, etc.)

- Development of quality control measures for compound purity and identity
  - separate contract for characterizing compounds by NMR and LC/MS to confirm identity of submitted compounds and to rule out degradation in transit

- Improved communication with University of Utah ASP scientists
  - discussions regarding assay results and best approaches to the screening workflow for submitted compounds
NINDS Anticonvulsant Screening Program (ASP)  
working group report and update

**Implementation update: recent changes and plans, cont.**

- Integrating ASP into NINDS epilepsy research program
  - Joint meetings with epilepsy program directors
  - Epilepsy program directors to visit the University of Utah in July

- Improved coordination between ASP and CounterACT
  - Joint meetings, plans for shared staff (countermeasures track)

- ASP leadership recruitment
  - Seeking *in vivo* pharmacologist with broad translational research experience; responsibility for ASP and other NINDS preclinical pharmacology efforts