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

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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

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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 ~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

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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.

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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

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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