# Mechanisms of action of anti-seizure drugs and the Anticonvulsant Screening Program of the National Institute of Neurological Disorders and Stroke

Roger J. Porter[1], Harvey J. Kupferberg[2], and Bettie Jean Hessie[3]

[1]Department of Neurology, University of Pennsylvania, Philadelphia, PA, and Department of Pharmacology, Uniformed Services University of the Health Sciences, Bethesda, MD, [2]Kupferberg Consultants, LLC, Rockville, MD, and [3]Consultant, Life Sciences Research, North Bethesda, MD, USA

**Abstract.** Objective: To determine the efficacy of the Anticonvulsant Screening Program (ASP) of the National Institute of Neurological Disorders and Stroke (NINDS) in identifying new anti-seizure drugs with new mechanisms of action (MOA). The ASP does not itself identify the nature of the MOA, but on further basic investigation, many of these drugs prove eventually to have a wide variety of new and novel MOA. Methods: Data were tabulated from multiple sources, including the ASP and the literature. Results: Since it was established in 1975, the ASP has contributed to the identification of at least 9 new anti-seizure drugs. The effectiveness of the program was evaluated by ascertaining the number of MOA of the anti-seizure drugs discovered by the ASP screening techniques. Considering the MOA of drugs marketed after 1975 – and the MOA of investigational compounds not yet marketed – the ASP has contributed to the identification of anti-seizure drugs that possess 16 distinctly different MOA. Conclusion: The ever-evolving screening approach of the ASP has many characteristics of a final common pathway for anti-seizure drug discovery.

## Introduction

The Anticonvulsant Screening Program (ASP) of the National Institute of Neurological Disorders and Stroke (NINDS) was established in 1975 to address the need for new anti-seizure drugs [1]. According to a working group report in 2012 (http://www.ninds.nih.gov/research/asp/asp_working_group_report_022712.htm), the ASP has contributed to the identification of 9 new anti-seizure drugs in the past 4 decades. To date, the program has screened more than 30,000 com-

pounds. The program's screening protocol continues to offer great promise for finding new anti-seizure drugs. This ongoing effort aims to provide, in the near future, more effective therapy for epilepsy through incremental improvements in the symptomatic treatment of seizures. Unfortunately, epileptic seizures are unlikely to be alleviated any time soon by disease-modifying or current anti-epileptogenic approaches [2].

A criticism of any drug screening program is that the effort will only uncover those drugs that are similar in clinical spectrum and MOA to the established drugs identified with similar screening assays. The ASP has not been immune to this criticism. However, one must consider that nearly 30% of patients with epilepsy could benefit from the development of more efficacious and better-tolerated drugs to treat their seizures. Despite the ASP limitations, the current screening approach, which continues to evolve with the introduction of different animal models of epilepsy, has been highly successful in identifying new anti-seizure drugs. The research community is working hard to develop and define a validated pathway for the discovery of effective therapy for patients with refractory seizures, a population as heterogeneous as all the different types of epilepsy [3, 4]. In the interim, we must continue our relatively empirical approach to identifying and developing new drugs. Much like the slow advances in the development of cancer chemotherapy, each new anti-seizure drug adds an increment to the armamentarium and helps some patients. The new anti-seizure drugs developed in the