Preface

Despite the introduction of several novel antiepileptic medications to the clinical practice during the last 20 years, the proportion of patients failing to achieve a seizure-free status has not improved substantially. Furthermore, current antiepileptic drugs provide symptomatic control to responsive patients (anticonvulsive or antiseizure effect) but have not proven to prevent the setting and progression of the disorder (antiepileptogenesis). Leading experts have emphasized the need for paradigm shifts in the field of antiepileptic drug discovery as a key factor to arrive at truly innovative therapeutic solutions. Such innovative solutions involve a wide and multidisciplinary array of strategies, including, among others, the development of new in vitro and in vivo models of epilepsy, the exploration of new molecular targets and mechanisms of action, the integration of computer-aided approaches, and the development of advanced drug delivery systems. Even though remarkable (yet incomplete) progress has been made in the knowledge of the pathophysiology of epilepsy and the determinants of refractoriness, these advancements have so far not crystallized into more efficacious therapeutic strategies. What is more, the epilepsy field has fallen somewhat behind regarding the integration of modern drug development tools, in comparison with other complex disorders such as cancer or Alzheimer's and Parkinson's diseases.

This volume aims to provide medicinal chemists, pharmacologists, and other scientists involved in antiepileptic drug discovery with a comprehensive view of novel approaches for the development of antiepileptic therapies, with a focus on novel molecular targets for antiepileptic drugs, computer-aided approaches for the identification of new drug candidates, and therapeutic strategies to overcome refractory epilepsy. The last part illustrates the potential benefits that network pharmacology and rational drug repurposing could bring to the antiepileptic drug discovery community.

The volume is made up of 19 chapters that are briefly commented on next.

Firstly, López-Meraz et al. describe the role of proinflammatory cytokines in the neuroinflammation process associated with seizure activity. They indicate the relevance of considering these cytokines as potential therapeutic targets for the pharmacological treatment of epilepsy. Valle-Dorado et al. present a review of different anti-inflammatory drugs that may be used to avoid the neuroinflammation that results from seizure activity. These authors suggest that anti-inflammatory drugs represent a strategy to decrease the higher excitability associated with epilepsy. Mendoza-Torreblanca et al. describe some of the basic aspects of the role of synaptic vesicle protein 2A (SV2A) in epilepsy, and support that this molecule is a good molecular target for the design of new antiepileptic drugs. Interestingly, they also provide an immunochemical protocol to obtain reliable semi-quantitative data of SV2A as well as a methodology to develop SV2A molecular dynamics simulations. Zavala and Rocha explain the relevance of evaluating the pro- and anticonvulsant effects of cannabinoids, depending on the type of epilepsy and the rate of excitability. Cuellar-Herrera et al. examine the importance of the pharmacological blockade of glutamate receptors as a therapeutic strategy to control seizure activity and induce neuroprotection. Gavernet discusses the existing evidence of the potential use of carbonic anhydrase as an antiepileptic drug target, describing a structure-based procedure for the design of novel inhibitors. Joshi and Kapur

describe experimental evidence supporting the idea that neurosteroids regulate seizure activity via modulation of $GABA_A$ receptors. They also provide data that neurosteroids represent a novel target to control seizure activity in women with epilepsy. Marelli et al. describe the mechanisms involved in the neuroprotective effects induced by erythropoietin and propose that the activation of its receptor (EPO receptor) can be used as a therapeutic strategy to avoid epileptogenesis and pharmacoresistant epilepsy. The last two chapters of the first part of the volume are dedicated to treatment options different from traditional small molecule therapies. Carvajal Aguilera and Phillips Farfán review different eating regimes used to control seizure activity and the mechanisms involved in their effects. They propose that elucidating the underlying mechanisms of these therapeutic interventions could help in the development of innovative antiepileptic medications, and they provide a protocol for the preclinical study of caloric restriction. López-García et al. provide a review of different gene therapies considered as possible strategies to reduce seizure activity.

In the second part, Lara et al. present an overview of the relevance of using human brain tissue to evaluate the pharmacoresistance in epilepsy and describe protocols of different approaches to fulfill this goal: in vitro electrophysiological recordings, in vitro procedures for receptor evaluation, and genomic analyses. Rogel-Salazar and Luna-Munguia analyze the role of the blood-brain barrier in epilepsy and the relevance of considering this structure as a target to design new antiepileptic strategies. Talevi and Bruno-Blanch describe the general procedures to implement a ligand-based virtual screening campaign for the identification of novel antiepileptic drugs. Couyoupetrou et al. also discuss technical aspects of computational (ligand-based) and experimental approaches used for the early detection of substrates of efflux systems, which could assist in the development of new antiepileptic drugs addressing the transporter hypothesis of pharmacoresistant epilepsy. Similarly, Palestro and Gavernet describe structure-based approaches that can be used to predict P-glycoprotein substrates. At the end of the second part of the volume, Ruiz and Castro examine the potential use of pharmaceuticals' micro- and nanocarriers to improve central nervous system bioavailability of antiepileptic agents; they also provide an experimental procedure to study drug release from such advanced pharmaceutical vehicles in vitro.

In the last part, Kubova presents a review of the different side effects induced by the different antiepileptic drugs and points out the necessity to carry out comparative, well-designed, and long-term trials in order to identify the best pharmacological strategy to control epilepsy. This author also emphasizes some reported beneficial effects of known antiepileptic drugs on comorbid mood disorders. In the two final chapters of the book, Talevi discusses the potential of network pharmacology and drug repurposing in the field of antiepileptic drug discovery, along with some practical consideration on how these approaches could be integrated into the drug discovery process.

The editors consider this book to be an excellent tool for the study of pharmacoresistant epilepsy and the discovery of new antiepileptic drugs.

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