Editorial

Effective and Promising Treatments for Neurological Disorders and Cancer

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Discovery and development of drugs with clinical efficacy presents a tremendous intellectual and commercial challenge. Many disorders remain untreatable and continue to cause incalculable losses to productivity, independence and overall quality of life among patients globally. However, the search for effective drug therapies cannot be the sole responsibility of the pharmaceutical industry because patients and business do not share the same level of tolerance for risk. The pharmaceutical industry is not as enthusiastic as patients about additional investments in drug design, research and development if the probability of success is low or even uncertain. Indeed, it is alarming that pharmaceutical companies are losing enthusiasm for developing effective treatments for challenging health problems, such as stroke, Alzheimer's disease, traumatic brain injury and certain types of cancer. An important reason for that unfortunate trend is a long record of failures at pre-clinical and clinical trials. How much enthusiasm is left? Does academia share this growing pessimism of the pharmaceutical industry? Why are effective drug treatments unavailable for critical neurological disorders and certain types of cancers after tremendous efforts and funds have been invested? What needs to be done to allow an early identification of effective drugs, therapies and their advancement to fast track clinical trials and delivery to drug stores? In the absence of unconditional dedication of the pharmaceutical industry to patients, it becomes a responsibility of academic and small start-up pharma supported by national and private health institutions to take the initiative of advancing novel high-risk-high-reward therapies.

This thematic volume is a result of an honest and evidence-based discussion initiated to predict what is coming next in this important medical field. It is an invited contribution of international experts in neurological disorders and cancer. Each manuscript is an independent input, not necessarily linked to any other manuscripts of the same volume. However, all articles share the same prime focus in addressing current challenges and opportunities in development of treatments for neurological disorders and cancer. The main emphasis is given to cholinergic strategies [1-8, 10-19] for sensorimotor [3, 4, 10, 11, 19] and cognitive [3-15] disorders associated with cholinergic hypofunction as well as neurotrauma [10, 11, 19] and cancer [1, 16-18]. In addition, serotonergic drugs are discussed as promising treatments for Alzheimer's disease [9] and schizophrenia [12].

The volume opens with an introductory article by Schroeder, Wecker and Philpot [1]. In this article, the authors discuss an alarming decline in research investment in treatment of central nervous system disorders and cognitive deficits related to cancer and/or cancer treatment. The authors identify therapeutic opportunities that arise from the current lack of effective cholinergic interventions for cognitive disorders.

Uteshev [2] then explores the concept of allosteric modulation and how it can be used to augment endogenous cholinergic tone to offset cholinergic hypofunction and thereby, restore cognitive, autonomic and immune homeostasis.

In the next article, Young and Wecker [3] focus on specific therapeutic benefits, challenges and limitations of cholinergic nicotinic treatments in neurological disorders associated with alterations in gait and balance, such as Parkinson's disease and hereditary ataxias.

The perspectives and clinical implications of cholinergic mechanisms and treatments in cognitive (e.g., Alzheimer's disease and schizophrenia) and sensorimotor (e.g., Parkinson's disease) disorders are comprehensively discussed by Fuenzalida, Pérez and Arias [4].

Thomsen, Andreasen, Arvaniti and Kohlmeier [5] then focus on the role of protein-protein interactions in current and future nicotinic treatments of Alzheimer's disease with a specific emphasis on Lynx proteins, NMDA receptors, β-amyloid, and the Wnt/β-catenin pathway.

This analysis is followed by a detailed discussion of the role of neuroinflammation in Alzheimer's disease and anti-inflammatory efficacy of α7 nicotinic acetylcholine receptor activation by Skok and Lykhmus [6].

In the next article, promising novel therapies for Alzheimer's disease including the use of nanoparticles, liposomes and stem cells are discussed by Confaloni, Tosto and Tata [7].

The therapeutic potential of drugs that enhance activation of α4β2 nicotinic acetylcholine receptors has not been adequately appreciated despite existing strong evidence supporting α4β2-dependent pro-cognitive and analgesic efficacies. A recent development of therapeutically promising positive allosteric modulators of α4β2 nicotinic acetylcholine receptors is discussed by Pandya [8].

While drugs that enhance cholinergic neurotransmission serve as effective tools in treatments of cognitive and sensorimotor deficits associated with various types of dementia, a number of serotonergic ligands proved to be effective in improving cognitive functions in Alzheimer's patients in recent clinical trials. Promising serotonergic approaches to treatments of Alzheimer's disease are analyzed in detail by Werner and Coveñas [9].

Neurological deficits often arise from ischemic and/or traumatic brain injuries. Targeting the cholinergic system following neurotrauma is discussed by Huber, Uteshev and Pauly [10].

The cholinergic potential, promising strategies and challenges in treatment of traumatic brain injury is the main focus of the following article by Uteshev, Tenovuo and Gaidhani [11].

The next article by Nikiforuk [12] opens a discussion on effective and promising cholinergic and serotonergic treatments of schizophrenia. It reviews the recent data from pre-clinical and clinical trials with the prime focus on ligands of α7 nicotinic acetylcholine receptors and serotonergic 5-HT5-7 receptors.

One way to increase the probability of success in clinical trials for psychiatric drugs is to effectively identify biological targets early in the process. Functional magnetic resonance imaging (fMRI) is a promising approach to this challenge. The update on the use of fMRI in psychiatric drug development is provided by Wylie, Smucny, Legget and Tregellas [13].

The therapeutic promise of nicotinic and muscarinic agonists and positive allosteric modulators in treatment of schizophrenia is the highlight of the next article by Gibbons and Dean [14]. The authors specifically focus on the roles of α7 nicotinic acetylcholine receptors and m1/m4 muscarinic acetylcholine receptors.

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An in-depth analysis of structure-affinity and structure-activity relationships for SEN12333, a novel promising chemotype of α7 nicotinic acetylcholine receptor agonists, is presented by Beinat, Banister, Herrera and Kassiou [15]. This lead structure may give rise to a variety of ligands with therapeutic efficacy in schizophrenia and Alzheimer's disease.

The next section of this thematic volume is dedicated to cholinergic signaling, mechanisms and therapeutic targets in treatments of cancer. This section includes three articles. First, Spindel [16] presents a comprehensive analysis of nicotinic and muscarinic acetylcholine receptor signaling and targets in lung cancer. This work is then extended by a focused discussion of the role of nicotinic acetylcholine receptors, mechanisms and treatments in lung cancer by Mucchietto, Crespi, Fasoli, Clementi and Gotti [17]. The section concludes with a comprehensive analysis of muscarinic acetylcholine receptors as targets for metronomic therapy in breast cancer by Sales [18].

Finally, a comprehensive analysis of neuroprotective strategies in glaucoma is given by Gossman, Christie, Webster, Linn and Linn [19]. These include both cholinergic and non-cholinergic approaches and provide an up-to-date review of neuroprotective therapies for the prevention and treatment of the loss of visual functions associated with glaucoma.

As this project is approaching its final stage, I am optimistic that the discussion it has initiated will continue to stimulate a positive attitude and drive towards therapeutic targets that meet high standards of clinical and social demands. I am pleased to see that this tribune was enthusiastically used by the authors and I hope that their unique views on challenging topics of drug development and guidance towards resolution of pharmaceutical failures will find an adequate positive response among readers.

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