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Editorial Article

Thinking Out of the Box for Next-Generation Drugs in Neurology

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Editorial

Pharmaceutical companies are currently facing unprecedented challenges associated with consequences of the last global financial crisis, patent cliff,loss in revenues from blockbuster drugs, etc. [1,2]. Research programs in neurosciences are particularly affected by this turmoil.

Indeed, some Big Pharma have recently reduced R&D activities in neurosciences and even shut down their programs because CNS drugs (i.e., except those for psychiatric indications), are probably among the riskiest, hardest and most expensive to develop – e.g., a long tradition of low approval rates for New Molecular Entities (NMEs), low efficacy, significant side effects, etc. [3,4].

In fact, there is still no medicine approved by regulatory authorities that can cure or significantly improve functions in patients with Spinal Cord Injury (SCI), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), Huntington's disease, neuropathic pain, Parkinson's Disease (PD) (except for levodopa) or Alzheimer's disease (AD) [5]. More than 1 billion people worldwide still suffer from diseases of the CNS [6].

Several reasons may explain this lack of potent CNS drugs – i.e., failure, at least until now, of stem cells or other repairing approaches as well as blood brain barrier issues associated with a limited access of many candidate medicines (except those with very small molecular weight) to target-brain cells.

Although several new approaches are currently being explored to de-risk and/or to improve the rate of approval of CNS drugs, one that may be considered as of particular interest is the multi-target approach. In brief, the latter could be characterized simply as an approach that consider and study CNS diseases as complex and multi-target problems, instead of simple mechanisms with single targets. The multi-target approach explores the effects of combinatorial therapies (drug-device or drug-drug) for enhanced efficacy or synergistic effects through complementary action mechanisms [7].

For instance, in AD research, single targets associated with the amyloid cascade have attracted most of the attention in recent years. However, within that cascade, multiple pathways could be targeted with combination therapies to help balance the risk and increase the probability of at least one approach being successful. A cocktail of active molecules could be used to increase the activity of α-secretase through agonism of Gq-coupled M1 receptors and inhibit β- or γ-secretase activity or stimulate proteases that are important in Aβ catabolism such as neprilysin and plasmin [8-10].

In PD research, there has been compelling evidence showing that levodopa-induced effects are superior when patients are also given specific serotonergic or dopaminergic receptor agonists (e.g., sarizotan, rotigotine) [11,12].

Moreover, for the recovery of some walking capabilities in patients with SCI, reactivating concomitantly5-HT1A receptors and D1 receptors associated with lumbar spinal cord neurons can reactivate 'dormant' spinal circuits capable of producing neural activities that underlie basic locomotion [13,14]. A comparable approach has also been used to temporarily restore bladder and bowel control reflexively after SCI [15,16].

In conclusion, the 'one-target-one-disease' principle, for which corresponding NMEs and monotherapies have been the end result for decades, has generally failed in developing potent CNS drugs [17]. The industry is bound, more than ever, to seek and choose new models for future innovation and sustained sales [18,19]. Identifying multi-target mechanisms and developing drug-drug combinations (e.g., fixed-dose combination products also known as FDCs) may yield improved approval rates and potent new therapies. In fact, in other areas such as asthma, HIV, cancer

or diabetes research, FDCs such as Atripla®, Advair®, Janumet®, to name a few, have become gold-standard therapies [17-19].

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