Introduction

Introduction to The Special Issue: Novel Molecular Pathways and Therapeutic Challenges in Neurodegenerative Diseases

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Neurodegenerative disorders, such as Alzheimer's disease, (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), present complex etiologies and pathologies. The lack of early detection is due to the absence of precise biomarkers [1–3]. The clinical management of these brain disorders has become more complex and challenging because the absence of precise novel biochemical drug targets has hindered discovery of new drugs [4–6]. One of the key issues is the increased incidence of neurodegenerative disorders in the world population, primarily due to an increase in life expectancy [4]. Despite an enormous upsurge in our understanding of the cellular and molecular pathways associated with cell death, the key molecular determinants to modulate these processes in human diseases is still not revealed, hindering the development of effective treatments and prevention avenues for aging and neurodegeneration [7–10]. In the near future, many new innovative approaches are needed to understand novel molecular pathways and therapeutics in neurodegenerative diseases. The current supplemental issue is a topical collection of focused thematic reviews and research papers on novel molecular pathways and therapeutic challenges in neurodegenerative diseases.

The Guest Editors for this special issue are: Dr. Jagannatha Rao KS, PhD, Panama and India; Dr. Lezanne Ooi, PhD, Australia; Dr. Muralidhar Hegde, PhD, USA; Dr. Yan Zhang, PhD, China; Dr. Nancy Y. Ip, PhD, Hong Kong; Dr. Mohammad Nami, PhD, Dubai and Iran; Dr. Mikko Hiltunen, PhD, Finland; Dr. John Jia En Chua, PhD, Singapore; Dr. Cecilia Bouzat, PhD, Argentina; and Dr. Samuel J.K. Abraham, MD, PhD, Japan.

The articles featured in the supplemental issue are fascinating and provide new thoughts to inspire young minds to plan future work. Our dream vision is focusing on how to reduce the burden of brain disorders by 2050, which is estimated to be 155 million. Now is the time to think innovatively to discover new pathways for future brain studies. The articles published in the present issue are divided under the following themes:

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THEME 1: NOVEL SMALL MOLECULES WITH NEUROPROTECTION PROPERTIES

Alzheimer's disease contains complex pathology, and drug discovery targets remain unclear. The current studies open new ideas in this direction. Particularly, Zhang and Jia [11] show novel findings on the role of betaine in modulating amyloid-β associated neuroinflammation through the reduction of the NLRP3 and NF-κB signaling pathways in microglial cells. Mansor and colleagues [12] provide new mechanistic pathways in understanding how *Centella asiatica* attenuates cell damage through oxidative stress. Additionally, Hui et al. [13] highlight the significant role of interferon-α in modifying the metabolic pathways in neuronal cell death. Ishabiyi and co-workers [14] developed a novel computational evaluation methodology to assess *Azadirachta indica*-derived bioactive compounds as potential inhibitors of the NLRP3 pathway as a possible treatment for AD. This study may lead to novel ideas for potential drug discovery. In an article by Daly et al. [15], they give insight into understanding the association with intervention; the Alzheimer's Disease-Associated Processes and Targets (ADAPT) ontology provides a new dimension to understanding novel neurodegenerative pathways. Furthermore, Castillo and colleagues [16] highlight the neuroprotective properties of eudesmin, a natural lignin from the tree *Araucaria Araucana*. This lignan prevents amyloid-β peptide toxicity in cell models and may lead to novel molecules in therapeutic intervention. Shirgadwar and team [17] identify a neuroprotective role of Phloretin in the rotenone-induced mice model of PD through the modulation of mTOR-NRF2-p62 mediated autophagy. This study further explains novel results for future development. Surya et al. [18] provide novel evidence on resveratrol-mediated regulation of hippocampal neurogenesis via the Wnt signaling pathway and provide novel neurotherapeutic implications.

THEME 2: NOVEL THERAPEUTIC APPROACHES OTHER THAN CHEMICAL MOLECULES

In this section, Li et al. [19] provide new ideas on acupuncture therapy for dementia and give insights on an integrated analysis of novel therapeutic mechanisms. Additionally, Yeap and colleagues [20] give new insight into BACE2 as a promising neuroprotective target for AD in targeting novel biosimilars. Chen et al. [21] examine the novel role of neural stem cells in the possible treatment of AD and highlight prospects for stem cell therapy. Tryphena and team [22] address the role of microRNAs in mitochondrial dysfunction and its novel role in future therapeutics in PD. Elzayat and colleagues [23] explained the novel role of miRNAs and stem cells as a possible promising diagnostic and therapeutic basis for AD, thus opening new insights.

THEME 3: ROLE OF GUT MICROBIOTA IN NEURODEGENERATION THERAPEUTICS

The findings in this theme include an article by Huang et al. [24] providing an understanding of the novel strategy for AD treatment based on the regulatory effect of amyloid-β on gut flora. Additionally, Raghavan and colleagues [25] report new findings on the beneficial role of beta 1,3-1,6 glucans on gut microbiota, alpha-synuclein expression, and amyloids-producing enterobacteria through a clinical pilot study of autism and in neurodegenerative diseases. This study provides new insight into the role of gut microbiome in different neurological disorders.

THEME 4: NEW AND NOVEL METABOLIC PATHWAYS IN NEURONAL CELL DEATH INCLUDING NOVEL BIOMARKERS

In this section, Liew and team [26] highlight the role of neuroinflammation interlinking the common pathways between epilepsy and AD. Zhao et al. [27] discussed the significant role of S-adenosylmethionine on cognition in animals and humans through meta-analysis of randomized controlled trials. Additionally, Roshan et al. [28] explain in detail the pathogenetic signature and aberrant neurogenic events in experimental cerebral ischemic stroke and provide new evidence on genomic signatures. Li et al. [29] highlighted the associations between insulin-like growth factor-1 and resting-state functional connectivity in cognitively unimpaired midlife adults. Chand Basha and team [30] reveal an outstanding link between TREM2 and microglia as a novel pathway in pathophysiology in AD. Next, Huang and colleagues [31] discuss the role of microglia-mediated neurovascular dysfunction in

AD. Guo and team [32] highlight the novel roles of meningeal lymphatic vessels in AD, while Zhang et al. [33] highlight the significant role of necroptosis in AD and its relevance for novel biomarker discovery and future drug targets. Krishna and colleagues [34] provide new dimensions on pathological dissimilarities in neuronal exosome-derived synaptic networking between AD and frontotemporal dementia. Additionally, Naren et al. [35] give insights into the key role of mitochondria health in brain disorders and provide new ideas on mitochondrial integrity and healthy functional mitochondria as key in brain health. Wong and Chow [36] link the role of neuronal cell senescence in brain aging and alterations in metabolic pathways that lead to neuronal cell dysfunction in AD. Finally, Chhimpa and team [37] review the role of mitochondrial citrate synthase in the pathogenesis of AD and its relevance to energy metabolic imbalance.

In summary, this special issue encompasses various pioneering approaches to understanding neurodegenerative diseases. With a series of studies, it explores novel molecular pathways, potential therapeutic targets, non-chemical treatments, and the role of gut microbiota and metabolic pathways in neurodegeneration. Each study contributes uniquely, offering fresh perspectives on neuroprotection properties, disease-modifying strategies, and potential biomarkers in neurodegenerative conditions. The supplemental issue thus represents a significant stride in the ongoing exploration of neurodegenerative diseases. It delivers a wealth of insights that enhance our comprehension of these conditions, providing hope for a brighter future in neurotherapeutics. The promising developments presented herein underscore the urgency and potential in neurodegenerative research and illuminate our path towards overcoming these challenging health issues by 2050.

The Guest Editors sincerely believe that the articles included in this issue shed new light in understanding novel pathways in neurodegeneration which may open new pathological events, novel biomarkers, new drug targets, and a new hope for the best clinical management. We all know that the burden of brain disorders is going to be key health challenge by 2050 and this issue provides new directions in both basic and clinical research innovations.

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