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Managing Strategies for Diverse Diseases: Challenges from Bench to Bedside Translation in Successful Drug Discovery and Development

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In today's era of sophisticated biotechnology and medical sciences, numerous thousands of ongoing research projects are simultaneously being undertaken across different private, academic and Government laboratories around the world. Advances are being made in each, but how does one optimally combine and focus them to maximize their united impact on disease treatment? The aim of this special issue of Current Pharmaceutical Design (CPD) is to aid medical research in this endeavor by providing articles to overview current progress and future perspectives focused towards management strategies for diverse diseases. Particular challenges facing numerous laboratories are those that involve laboratory bench to clinical bedside translation in the path of successful drug discovery. Are there ways to optimize this across disorders; are there rules that best should be followed? Authors of this special issue were requested to provide a review article sufficient to provide a beacon to identify guidelines for clinically translatable research that can improve both the time and success rate that treatment can reach its public health goals, globally. Of interest are articles pertinent to type 2 diabetes mellitus, cancer, inflammation & immunological disorders, infectious diseases, neurodegenerative disorders - particularly Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis - and neuropsychiatric disorders. Our initial intention was to publish all articles within a single special issue of CPD. However, on receiving so much interest from contributors, our request to the Editor-in-Chief of CPD for permission for a second part to the special issue has been approved. Yet further interest has resulted in approval for development of a third part. The schedule for submission of manuscripts to the office of CPD by guest editors is April 2016 and September 2016 for Part-2 and Part-3, respectively.

In this issue, Ghandadi *et al.* [1] review the role of interleukin-6 (IL-6) as a critical cytokine in cancer multidrug resistance (MDR). The most consistent feature in MDR is overexpression and/or overactivity of ATP-dependent drug efflux transporters. Other mechanisms such as overexpression of drug-detoxifying enzymes and alterations in pro-survival or pro-death signaling pathways are also responsible for MDR. Inflammatory mediators including IL-6 play important roles in various events during inflammation and are

also involved in development and progression of several types of cancers. Mounting evidence has suggested a crosstalk between IL-6 and MDR in cancer, highlighting the role of IL-6 in chemotherapy response, and the potential opportunity to control MDR through modulation of IL-6 expression. Conversely, IL-6 inhibition using different strategies (antibodies, siRNA, and antisense transfection) has been shown to improve tumor responsiveness and mitigate MDR in different cancer cell lines. Their review focuses on the *in vitro*, experimental and clinical findings on the role of IL-6 in MDR, and potential therapeutic opportunities arising from the role of IL-6. IL-6 has a central role in the pathophysiology of different types of cancer by influencing different developmental stages of cancer including MDR and metastasis. Their manuscript topic has certainly great biological and clinical importance. According to one of the referees, it is an exhaustive and timely review on a topic which is hot indeed.

Mushtaq *et al.* [2] explore neuroprotective mechanisms mediated by Cyclin-dependent kinase 5 (CDK5) inhibitions. CDK5 is a proline-directed serine/threonine kinase belonging to the family of cyclin-dependent kinases. In addition to maintaining the neuronal architecture, CDK5 plays an important role in the regulation of synaptic plasticity, neurotransmitter release, neuron migration and neurite outgrowth. Although various reports have shown links between neurodegeneration and deregulation of cyclin-dependent kinases, the specific role of CDK5 inhibition in causing neuroprotection in cases of neuronal insult or in neurodegenerative diseases is not well-understood. They discuss current evidence for the involvement of CDK5 deregulation in neurodegenerative disorders and neurodegeneration associated with stroke through various mechanisms. These include upregulation of cyclin D1 and overactivation of CDK5 mediated neuronal cell death pathways, aberrant hyperphosphorylation of human tau proteins and/or neurofilament proteins, formation of neurofibrillary lesions, excitotoxicity, cytoskeletal disruption, motor neuron death (due to abnormally high levels of CDK5/p25) and colchicine-induced apoptosis in cerebellar granule neurons. A better understanding of the role of CDK5 inhibition in neuroprotective mechanisms will help scientists and researchers to develop selective, safe and efficacious pharmacological inhibitors of CDK5 for therapeutic use against human neurodegenerative disorders, such as Alzheimer's disease, amyotrophic lateral sclerosis and neuronal loss associated with stroke.

Dar *et al.* [3] report unique medicinal properties of *Withania somnifera* (WS) with respect to its phytochemical constituents and protein component. It is an important medicinal herb that has been widely used for the treatment of different clinical conditions. The overall medicinal properties of WS make it a viable therapeutic agent for addressing anxiety, cancer, microbial infection, immunomodulation, and neurodegenerative disorders. Biochemical constituents of WS like withanolide A, withanolide D, withaferin A and withaniamides play an important role in its pharmacological properties. Proteins in WS such as glycoprotein and withania lectin like-protein possess potent therapeutic properties like antimicrobial, anti-snake venom poison and antimicrobial. In this review, they tried to present different pharmacological properties associated with different extract preparations, phytochemical constituents and protein component of WS.

In an intriguing review, Alam *et al.* [4] shed light on inflammatory process in Alzheimer (AD) and Parkinson's diseases (PD) via central role of cytokines. Numerous evidences have established the role of neuroinflammation in the AD and PD pathology. The inflammatory components such as microglia, astrocytes, complement system and cytokines are linked to neuroinflammation in the central nervous system. More specifically, cytokines have been found to play a central role in the neuroinflammation of AD and PD. A number of studies have demonstrated abnormally elevated levels of inflammatory cytokines such as interleukin-1 β (IL-1 β) and tumor necrosis factor (TNF) in AD and PD patients. Activated microglial cells have been shown to be involved in the secretion of pro-inflammatory cytokines such as IL-1, IL-6, TNF- α and the transforming growth factor- β , thereby contributing towards the progress of neurological disorders. Chronic inflammation caused by microglial cells is the fundamental process involved in the destruction of neurons associated with dopamine-production in the brain of PD patients. Hence, there is a need to explore the key inflammatory components in AD and PD pathogenesis in order to fully understand the root cause and establish a substantial link between these two disorders. Such knowledge will help in better management of AD and PD.

Solayman *et al.* [5] emphasize that polyphenols have potential future arsenals in the treatment of diabetes. Diabetes mellitus (DM) is one of the most common endocrine metabolic disorders. In addition to exercise and diet, oral anti-diabetic drugs have been used as a part of the management strategy worldwide. Many plants have been shown to act as anti-diabetic agents, in which the main active constituents are believed to be polyphenols. Natural products containing high polyphenol levels can control carbohydrate metabolism by various mechanisms, such as protecting and restoring beta-cell integrity, enhancing insulin releasing activity, and increasing cellular glucose uptake. Their review depicts a comprehensive picture on the available anti-diabetic polyphenols (medicinal plants, fruits and vegetables) with mechanisms involved in the anti-diabetic effects of polyphenols in the various pathways of DM. Additionally, the types of polyphenols that could be potential future resources in the treatment of DM via either novel regimens or as supplementary agents.

Jabir *et al.* [6] discuss current updates on therapeutic advances in the management of cardiovascular diseases (CVD). There are several treatment methods for CVD and associated complications that have been considered till now. The current treatment methods can't produce rapid cure, but could prevent or reduce the progression of this devastating disease. They summarized the use of various pharmacological agents viz. HMG-CoA reductase inhibitors (statins), antihypertensive, thrombolytic and anticoagulation agents that are currently used for the management of CVD which targets different biochemical or molecular events. Still more research in this field is advocated which will provide the rapid and effective treatment methods in order to avoid fatal complications associated with CVD.

Baig *et al.* [7] comment on computer aided drug designing to explore its success and limitations in the development of new drug molecules. Structure-based drug design and ligand-based drug design are two methods commonly used in computer-aided drug design. They discuss the theory behind methods and review structure based as well as ligand based virtual screening processes. Molecular Dynamics simulation, which has become one of the

most influential tools to predict the conformation of small molecules along with prediction of the model conformational changes within the biological target, has also been taken into account. The principles and concepts of molecular docking, pharmacophores and other methods used in computer-aided drug design have also been touched in their review.

Mir *et al.* [8] report structure, therapeutic potential and pharmacological applications of conotoxins. Cone snails, also known as marine gastropods, from *Conus* genus produce in their venom a diverse range of small pharmacologically active structured peptides called conotoxins. The cone snail venoms are widely unexplored arsenal of toxins with therapeutic and pharmacological potential, making them a treasure trove of ligands and peptidic drug leads. Conotoxins are small disulfide bonded peptides, which act as remarkable selective inhibitors and modulators of ion channels (calcium, sodium, potassium), nicotinic acetylcholine receptors, noradrenaline transporters, N-methyl-D-aspartate receptors, and neurotensin receptors. They are highly potent and specific against several neuronal targets making them valuable as research tools, drug leads and even therapeutics. In their review, they gave an overview of gene superfamily classification, nomenclature, post-translational modification, structural framework, pharmacology and medical applications of the active conopeptides. Understanding these aspects of conopeptides will help in designing more specific peptidic analogues.

Golmirzaei *et al.* [9] analyzed and discussed psychopharmacology of Attention-Deficit Hyperactivity Disorder (ADHD) in term of effects, side effects and mechanism of action. It is a common psychiatric disorder in children which manifests with hyperactivity, impulsivity, and/or inattention. Several drugs are used in treatment of ADHD. Stimulants, atomoxetine, anti-depressants, and bupropion are common medications used in the treatment of ADHD. Stimulants are widely used as the first line treatment in children with ADHD. Their mechanism of action is the release of dopamine and norepinephrine in central nervous system. Methylphenidate is the most common stimulant used for the treatment of ADHD. Methylphenidate significantly reduces ADHD symptoms in children both at home and school and improves their social skills. Methylphenidate is safe in healthy children and has shown to have no cardiac side effects in these patients. Other medications include: Atomoxetine, Amphetamines, Clonidine, Melatonin, and anti-depressants.

Sahebkar *et al.* [10] systematic review aimed efficacy and safety of evacetrapib for modifying plasma lipids and meta-analysis of randomized controlled trials. Evacetrapib, a new cholesteryl ester transfer protein inhibitor, is being investigated as a potential therapeutic option for reducing cardiovascular events through increasing high-density lipoprotein cholesterol (HDL-C) concentrations. Results of the meta-analysis suggested that evacetrapib, either as monotherapy or in combination with a statin, reduces LDL-C and increases HDL-C levels but has no effect on triglyceride concentrations. Adverse events appeared to be similar in subjects receiving evacetrapib and placebo in short-term follow-ups.

We wish to end this editorial by thanking **Dr. William A. Banks**, the Editor-in-Chief, as well as **Kazim Baig**, the Director of CPD, along with all the contributing authors who have passionately responded to our request by contributing to this special issue of CPD. We

additionally extend our thanks to all peer reviewers for their time and expertise in revising individual contributions to a consistently high level of distinction. Consequent to the combined efforts of such a great scientific team - remarkable for their extensive expertise across such a broad arena of diverse diseases - the current special issue provides the scientific and lay readers an important resource of reference in relation to drug development strategies to benefit both medical researchers with interest in as well as those suffering from neurological, cardiovascular and metabolic disorders.

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