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Frontier Views in Designing Therapeutic Candidates for Management of Diverse Diseases

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There is little doubt that humanity is still suffering from a huge burden of health issues in today's era of sophisticated technology and medical sciences, such as cancer, obesity, infectious diseases, neurodegenerative disorders and neuropsychiatric disorders. Each health issue can be categorized further as exemplified by cancer, which has numerous different categories; e.g. prostate cancer typically affects men over the age of 50. Thousands of new cases of prostate cancer are diagnosed in each country every year with family history playing a key risk factor. There are many topics to discuss on each disease, like pathology, causes, symptoms, risk factors, diagnosis, current management as well as new research to find best treatment strategies. The aim of this special issue of Current Pharmaceutical Design (CPD) was to aid pharmaceutical research in this endeavor by providing review articles for an overview of 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 in the path of successful drug discovery. Authors of this special issue were requested to present a review to identify guidelines for *in vitro* to clinically translatable research to enhance the success rate so treatments can reach the public health goals at a global level. The ensuing key words were indicated in the advertisement of call for this special issue: Alzheimer's disease, cancer, central nervous system, drug delivery systems, huntington, liver, microbiology, nanomedicines, neurodegenerative disorders, obesity, Parkinson's disease, type 2 diabetes mellitus, Infectious diseases, microbiota, virus, bioinformatics, natural/herbal products.

In this special issue of CPD, Ahmad *et al.* [1] review bile salt stabilized vesicles (bilosomes) as a novel nano-pharmaceutical designed for oral delivery of proteins and peptides. With the advent of novel vesicular drug delivery systems especially bilosomes, for large molecular weight proteins and peptides, their oral administration seems a viable approach. These nano-vesicles have shown promising results for the effective delivery of insulin and other therapeutics, perhaps due to their structural composition. The extensive search for such viable agents been presented related to the formulation, evaluation and *in vivo* performance of bilosomes. The successful drug delivery through bilosomes requires significant

justifications related to interaction with the biological membranes. Numerous other aspects such as absolute absorption, safety and toxicity of bilosome drug delivery should also be equally considered [1].

Panahi *et al.* [2] explore about sulfur mustard-induced ocular injuries to provide an update on mechanisms and management perspectives. Sulfur Mustard (SM; mustard gas) is a classic chemical warfare agent that has been used in several conflicts and is still a potential threat, especially in the Middle-East region. Victims experience acute symptoms in air-exposed organs including skin, respiratory tract and the eyes. Survivors of the acute stage might develop chronic or delayed-onset complications in the exposed organs. The exact mechanism(s) of SM-induced tissue damage is still unknown, however DNA alkylation and oxidative damage are the most relevant processes. The eye is the most sensitive organ to the SM vapor and ocular symptoms usually precede other manifestations. Ocular findings including blepharitis, dry eye disease, corneal vascularization, persistent epithelial defects, limbal ischemia, limbal stem cell deficiency, corneal thinning, corneal opacity and corneal innervation abnormalities have been reported several years after SM exposure. Panahi *et al.* [2] have also included recent advances in amniotic membrane transplantation, cultivated stem cell transplantation and anti-angiogenic therapies which might be considered as therapeutic options in SM-induced ocular damage in the future.

Islam *et al.* [3] report on therapeutic suppression of nonsense mutation, which focuses on an emerging target in multiple diseases particularly thrombotic disorders. Nonsense mutations contribute to approximately 10–30% of the total human inherited diseases via disruption of protein translation. If any of the three termination codons emerges prematurely (PTC) before the natural canonical stop codon, truncated non-functional proteins or proteins with deleterious loss or gain-of-function activities are synthesized, followed by the development of nonsense mutation-mediated diseases. In the past decade, PTC-associated diseases have captured much attention in biomedical research, especially as molecular therapeutic targets via nonsense suppression regimens. In this review, Islam *et al.* [3] have highlighted different treatment strategies of PTC, targeting readthrough therapeutics including the use of aminoglycosides, ataluren (formerly known as PTC124), suppressor tRNAs, nonsense-mediated mRNA decay, pseudouridylation and the CRISPR/Cas9 system to treat PTC-mediated diseases. In addition, as thrombotic disorders are a group of disease with major burdens worldwide, 19 potential genes containing a total of 705 PTCs that causes 21 thrombotic disorders have been listed based on the data re-analysis from the ‘GeneCards® - Human Gene Database’ and ‘Human Gene Mutation Database’ (HGMD®). These PTC-containing genes can be potential targets amenable for different readthrough therapeutic strategies in the future.

In an interesting review, Rasool *et al.* [4] have shed light on DARPins (designed ankyrin repeat proteins) as a platform for bioengineering and theranostic approaches for these interesting genetically engineered antibody mimetic proteins. The therapeutic significance of bioengineering proteins has increased dramatically in recent years, and DARPins are now considered as a new generation of pharmacological agents as they typically exhibit highly specific and high-affinity target protein binding and, thereby, have promising medical treatment possibilities. As naturally occurring ankyrin proteins can mediate high-affinity

protein-protein interactions in nature, DARPins libraries can be designed to provide sequence alignments to support the formation of a stable interaction with a large potential target to modify its physiological function, or potentially block a pathological one. In theory, DARPins can be generated to act as receptor agonists, antagonists or even inverse agonists, in addition to enzyme inhibitors or simple target protein binders to block access to other protein interactions. They combine the features of a relatively small size (~14 kDa) and high potency (often in the pM range) with a high thermal and thermodynamic stability, as well as pharmacokinetic stability - providing them attributes that immunoglobulins may lack. Together with a versatile scaffold to accommodate many scientific uses and cost efficient production, some have been developed to the clinic and the role of this technology in science and medicine is worth following [4].

Momtazi-Borojeni *et al.* [5] review the pharmacology and toxicology of steviol glycosides extracted from *Stevia rebaudiana*. *Stevia rebaudiana* Bertoni is a sweet and nutrient-rich plant belonging to the Asteraceae family. Stevia leaves contain steviol glycosides including stevioside, rebaudioside (A to F), steviolbioside, and isosteviol, which are responsible for the plant's sweet taste, and have commercial value across the world as a sugar substitute in foods, beverages and medicines. Among the various steviol glycosides, stevioside, rebaudioside A and rebaudioside C are the major metabolites and these compounds are on average 250–300 times sweeter than sucrose. Steviol is the final product of Stevia metabolism. The metabolized components essentially leave the body and there is no accumulation. Beyond their value as sweeteners, Stevia and its glycosides are reported to possess therapeutic effects against several diseases such as cancer, diabetes mellitus, hypertension, inflammation, cystic fibrosis, obesity and tooth decay. Studies have shown that steviol glycosides found in Stevia are not teratogenic, mutagenic or carcinogenic are not associated with acute or subacute toxicity. The Momtazi-Borojeni *et al.* [5] review provides a summary on the biological and pharmacological properties of steviol glycosides that might be relevant for the treatment of human diseases.

Javadi *et al.* [6] review medicinal plants for the treatment of asthma focus towards a Traditional Persian Medicine (TPM) perspective. The conformity of the TPM findings on the anti-asthmatic efficacy of plants with the findings of pharmacological studies was also explored. The scientific names of TPM-suggested plants were determined using botanical databases and were used for a multi-database electronic search in PubMed, Scopus, ScienceDirect and Google Scholar databases. Then, the anti-asthmatic effectiveness of TPM-recommended plants was verified in light of findings from modern pharmacological investigations. According to the main TPM texts, *Adiantum capillus-veneris*, *Boswellia oleogumresin*, *Crocus sativus*, *Glycyrrhiza glabra*, *Hyssopus officinalis* and *Ruta graveolens* were the most efficacious medicinal plants for the treatment of asthma. This was supported by pharmacological studies which showed counterbalancing effects of the above-mentioned plants on inflammation, oxidative stress, allergic response, tracheal smooth muscle cell constriction and airway remodeling. The strong ethnobotanical background of plants used in TPM could be a valuable tool to find new anti-asthmatic medications. TPM-suggested anti-asthmatic plants were found to possess several mechanisms relevant to the treatment of respiratory diseases according to the information retrieved from modern pharmacological

studies. This high degree of conformity suggested further proof-of-concept trials to ascertain the role of these plants in the routine management of asthmatic patients.

Sharma *et al.* [7] provide an update on factors, mechanism and regulation of the phosphoinositide 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) intracellular pathway and breast cancer. Recent research reveals that one in every eight women has been diagnosed with breast cancer. In the past few decades, extensive progress has been made in developing cytotoxic and targeted therapies against cancer, which have positively impacted survival rates. One of the targets, the PI3K/Akt/mTOR complex intracellular pathway, plays a significant role in breast cancer by leading to cell growth and further tumor proliferation. A number of inhibitors of the PI3K/Akt/mTOR pathway are already in clinical trials or under preclinical development. These inhibitors, either alone or in combination with cytotoxic agents, can be used for endocrine therapies. The Sharma *et al* [7] article provides an overview of the structure of mTOR, intracellular PI3K/Akt/mTOR pathway, and, more precisely, the role of this pathway in therapies linked to breast cancer.

Tran and Tran provide an insightful review focused on the perspective strategies using swellable polymers in solid dispersions for controlled drug release [8]. Poorly water-soluble drugs, which commonly face the issue of poor absorption and low bioavailability, have provided a focus of research of many formulation scientists for the past few decades. Solid dispersion is one of the most effective strategies for improving bioavailability of poorly water-soluble drugs. Indeed, either application of solid dispersions in dissolution enhancement of poorly water-soluble drugs or the use of swellable polymers in controlled drug release has been widely reported in the design of pharmaceuticals. Tran and Tran provide a summary of techniques used to formulate a swellable polymer in solid dispersion; especially a description of a suitable fabrication method in the design of a controlled release solid dispersion [8].

Sabouri-Rad reviewed experimental and clinical studies exploring the therapeutic efficacy of ginseng and ginsenosides in the field of dermatology [9]. Ginseng has gained fame as one of the most popular herbs originating from Eastern countries. Among different species which are known as ginseng, *Panax ginseng* C. A. Mey. is the most frequently used one. Ginsenosides have been proposed to account for most of the biological activities of ginseng. The widely appreciated health-promoting effect of ginseng pertains to the beneficial effects of this plant against immune, cardiovascular and sexual disorders and cancer. In addition, there are some new aspects of the pharmacological activity of this plant which justify its evaluation in dermatologic diseases. In dermatology, ginseng has been investigated mechanistically for its therapeutic effects in photo-aging, wound and injury, skin cancer, dermatitis, hair loss, alopecia and cold hypersensitivity [9].

Tiwari *et al.* [10] highlight *Gymnema sylvestre* for diabetes, which is a traditional herb and candidate future therapeutic. Diabetes has increased at an unprecedented rate and is fast emerging as a global health threat. The focus of pharmacological studies pertaining to diabetes has seen a remarkable shift from conventional medicines to therapeutics employing bioactive phytochemicals from natural sources. The potential effectiveness of natural products together with their low cost and generally well tolerated side effects has

revolutionized the entire concept of drug discovery and management programs. One such beneficial herb is *Gymnema sylvestre*, possessing remarkable hypoglycemic properties and forms the platform of diabetes therapeutics in the traditional system of medication. Tiwari *et al.* [10] discuss the significance of *G. sylvestre* in diabetes management, the herbal-formulations from the herb together with its standardization and clinical trials on animal models, and why Peroxisome Proliferator Activated Receptor gamma (PPAR γ) may serve as a prospective molecular target for Gymnemic acid analogues. Such studies help define the molecular basis of bioactive molecules and aid in development on natural product based therapeutics in the treatment of diabetes [10].

In closure, we end this editorial by thanking Dr. William A. Banks, the Editor-in-Chief, as well as Mr. Kazim Baig, the Director of CPD, along with all the contributing authors who have actively responded to our request by contributing to not only this and all three parts of the previous special issue of CPD on managing strategies for diverse diseases: challenges from bench to bedside translation in successful drug discovery and development [11–43]. We extend our appreciation to the peer reviewers for the time and expertise that each altruistically provided by revising individual contributions to a consistently high level of quality to allow completion of this special issue-2 of CPD. As a result of the combined efforts of this scientific team - notable for their extensive expertise across such a broad arena of diverse medical disorders and scientific technologies - the current special issue-2 provides to both the scientific and lay reader a valuable resource of reference for fast developing drug development strategies that possess substantial promise to benefit the community at large.

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