



Editorial



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



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In the fields of pharmacological, biotechnological and medical sciences, numerous billions of dollars are spent annually on basic and clinical research and development to better understand and promote global health. These funds support scientific, clinical and administrative salaries, chemicals, instruments and consumables, preclinical research and clinical trials, laboratory infrastructure and numerous other essential costs in relation multiple research projects undertaken across different laboratories around the globe, as science – like disease - knows no borders. Small and large scientific advances are continuously being made across areas, but how does one optimally combine and focus them to maximize their united impact on disease management. The goal of this special issue of Current Pharmaceutical Design (CPD) is to aid medical research



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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 tailor and optimize this across disorders; are there guidelines that best should be followed? Authors of this special issue were invited to generate a review article appropriate to describe technologies with potential value across diseases to provide a guiding light to identify courses of action and procedures for clinically translatable research that can both advance the success rate and shorten the timeline to support a treatment to positively impact public health goals, globally.

In this part C special issue of CPD, Rani *et al.* [1] review the pharmacological properties and therapeutic potential of naringenin. Naringenin, chemically known as 5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one, is a common dietary polyphenolic constituent of citrus fruits. This flavanone is prominently found in grapefruit and is receiving considerable attention in relation to its pharmaceutical and nutritional development. Accruing evidence from both *in vitro* and *in vivo* studies continues to unravel numerous biological targets along with complex underlying mechanisms indicative of the promising therapeutic application naringenin across various neurological, cardiovascular, gastrointestinal, rheumatological, metabolic and malignant disorders. Functionally, the bioactivity of naringenin is primarily attributed to its anti-inflammatory, immunomodulatory and anti-oxidant effects. The article by Rani *et al.* provides a comprehensive review of the various studies that have evaluated the therapeutic potential of naringenin and its actions at the molecular level. It valuably summarizes pharmacokinetic data and issues and challenges involved in pharmaceutical development, and suggests that naringenin represents an agent worth of further scientific investigation as, if appropriately optimized, it may represent a therapeutically valuable citrus flavonoid and useful dietary adjunct in treatment of a broad number of human ailments.

Ahmad *et al.* [2] reveal and explore the current understanding of engineered nanoparticles in relation to their use to combat multidrug resistance (MDR) in cancer. A variety of mono and combinational chemotherapies have been developed and gradually optimized over the years towards the effective treatment of cancer. However, the development of chemotherapeutic resistance or MDR in cancer is a constant and huge challenge to researchers facing successful chemotherapeutic use. MDR is a complex process combining multifaceted non-cellular and cellular-based mechanisms. Research in the area of cancer nanotechnology over the past two decades is at last moving to the point where smartly designed nanoparticles with targeting ligands can aid chemotherapy success through supporting the preferential accumulation of their contents in the tumor region by means of active and passive targeting. This can lower the off-target accumulation of the nanoparticle payload. Such nanomedicines are at different stages of clinical trials and are providing promising results in cancer therapy, including resistant cases. Nanoparticles as chemotherapeutic carriers offer the opportunity to have multiple payloads of drugs and/or imaging agents for combinational and 'theranostic' (sometimes termed theragnostics) therapy. The focus of such technology is to increase therapy success by (i) optimizing the efficacy of drugs so that more patients positively respond to them and, (ii) combining a potential diagnostic/prognostic tool to identify those patients that are most likely to respond, thereby minimizing potential non-responders from toxicities of drugs they would not benefit from. Such nanotechnology is continually extending into new scientific areas with new treatment strategies combining NIR, MRI and HIFU in cancer chemotherapy and imaging. Ahmad *et al.* [2] discuss cellular/non-cellular factors constituting MDR in cancer and the role of nanomedicines as an approach to combat MDR cases of cancers, combining payloads of agents in an innovative manner to hopefully maximize patient benefits.

Sacco *et al.* [3] report on challenges and strategies in precision medicine for non-small cell lung cancer (NSCLC). Lung cancer is the most common cause of cancer-related death worldwide, producing over 1.2 million deaths each year. NSCLC comprises of a group of malignancies that are pathologically and molecularly diverse, but that are all characterised by a poor prognosis and represent some 85% of all lung cancers. Survival rates for lung cancer patients have improved very slowly; but this is relatively modest as NSCLCs are relatively insensitive to chemotherapy, as compared to small cell carcinoma. While smoking is by far the leading risk factor for lung cancer, with the social stigma associated with smoking favourably impacting primary prevention, the disease continues to dominate as a leading cause of preventable

deaths; additionally, lifelong non-smokers can present with adenocarcinoma of the lung. In recent years, NSCLC has become an exemplar for precision medicine, mainly consequent to the development of drugs targeting the receptors of epidermal growth factor and anaplastic lymphoma kinase. Whereas epidermal growth factor receptor and anaplastic lymphoma kinase inhibitors are only applicable to a minority of patients and benefits are almost invariably short-lived, current studies indicate that at least 50% of patients with NSCLC have a potentially targetable mutation. With a growing armamentarium of inhibitors against these targets in development, there is a hope that a greater proportion of patients will benefit from precision medicine. However, there remain significant challenges in the development of precision medicine in NSCLC. These include: the identification and validation of new targets, ensuring that biopsies are fit for purpose, tumour heterogeneity, requirements for serial tumour assessments, and - not least - the cost and who should bear it. In their review, Sacco *et al.* [3] detail the current status of precision medicine in NSCLC, and describe how basic and translational research is paving the way towards overcoming the above challenges. In addition, clinical strategies with respect to liquid biopsies and the potential use of extracellular vesicles, such as exosomes, are discussed.

In an intriguing review, Momtazi and Sahebkar [4] shed light on difluorinated curcumin as a promising curcumin analogue with an improved anti-tumor activity and pharmacokinetic profile versus the parent agent. The natural product curcumin is a bright yellow polyphenol and the principal curcuminoid of turmeric that is a dietary phytochemical with a diversity of reported health benefits that include anti-tumor actions. Curcumin exists in keto and enol tautomeric forms, and the latter form undergoes a rapid metabolism resulting in its low oral bioavailability. Fluorination provides a potential approach to block generation of the enol form and improve the bioavailability and potency of curcumin. Fluorine substitution enhances metabolic stability and potency of anticancer agents consequent to the higher metabolic stability of C-F bonds, as compared with C-H or C-OH bonds. 3, 4-Difluorobenzylidene curcumin (CDF) is a novel fluorinated curcumin analogue that has been shown to be about 3-fold more bioavailable than curcumin. Biodistribution assays have revealed that curcumin is mostly distributed to the heart and lung tissues while CDF is preferentially accumulated in pancreas where its tissue concentrations reach 2-fold higher than those of curcumin. Moreover, CDF has been reported to possess stronger cytotoxic effects, compared with curcumin, in both monolayer and spheroid cultures of different tumor cell lines, including chemo-resistant ones. Mechanistic investigations have revealed that CDF can promote tumor suppression through multiple mechanisms. These encompass the inhibition of self-renewal capacity of cancer stem/stem-like cells, reducing the clonogenicity invasiveness and angiogenesis of tumor cells, and increasing the sensitivity of cells to chemotherapy. These effects are considered to derive from the modulatory action of CDF on diverse targets, such as miRNAs, PTEN, CD44, EGFR, EpCAM, EZH2, HIF-1 α , and VEGF. The Momtazi and Sahebkar article [4] provides an overview of the findings on metabolism and pharmacological activities of CDF, and underlines potential opportunities to use this novel curcumin analogue in the treatment of cancer.

Alam *et al.* [5] highlight DNA methylation in relation to its epigenetic impact on the development of Type 2 Diabetes Mellitus (T2DM). DNA methylation, a major regulator of epigenetic modifications, and has been shown to alter the expression of genes that are involved in aspects of glucose metabolism; thereby, impacting and potentially driving glucose intolerance, insulin resistance, β -cell dysfunction and other key conditions that can ultimately lead to the pathogenesis of T2DM. Current evidence supporting an association between DNA methylation and T2DM is critically evaluated by Adam *et al.* [5], as an understanding of the epigenome of diabetic patients may help to reveal otherwise hidden causes of this common progressive disease. In addition, an update of current approaches and their positive and negative attributes is provided as a basis for the adoption of suitable techniques to support future DNA methylation research towards better management of T2DM. In this regard, elucidation at a mechanistic level of the relationship between vital environmental factors and T2DM development appears to be warranted to both probe and better understand the rate determining molecular events.

Pervaiz *et al.* [6] highlight and review a series of alkaloids, naturally occurring chemical compounds that generally possess basic nitrogens, with a focus on an emerging antibacterial modality against Methicillin Resistant *Staphylococcus aureus* (MRSA). This Gram-positive bacterium is a member of the Firmicutes phylum of bacteria and is responsible for several increasingly difficult-to-treat infections in humans that are especially troublesome in hospitals, nursing homes and prisons, where patients are at a substantially high risk of nosocomial infection than the public at large. MRSA strains of *Staphylococcus aureus* develop via a process of natural selection, resistance mechanisms to β -lactam antibiotics (including methicillin, oxacillin, dicloxacillin and nafcillin) and cephalosporins. With synthetic drug/antibiotic treatments becoming less effective, natural products represent an emerging new alternative for future antibacterial drug development as their underpinning mechanisms of action and structures are different from classical antibiotics. The article by Pervaiz *et al.* [6] focuses on 32 alkaloids isolated from various plants that have provided promising antibacterial activity against MRSA by acting through divergent mechanisms and biological cascades.

Islam *et al.* [7] review the medical literature on antiphospholipid antibody-mediated thrombotic mechanisms in the development of antiphospholipid syndrome (APS) (sometimes termed 'Hughes syndrome'). This systemic autoimmune disease is characterized by a persistently high titer of antiphospholipid antibodies (aPLs). In addition to pregnancy morbidity, arterial and/or venous thrombosis is another key clinical feature of APS. Regardless of the type of APS, the thrombi formed by the induction of aPLs can lead to deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke and gangrene. Although the concept of APS was introduced some 30 years ago in the 1980s, its thrombogenic pathophysiology remains unclear. Therefore, patients are treated with anticoagulant and/or antiplatelet regimens, similar to other thrombotic disorders, even though APS thrombotic pathophysiology is mainly aPLs-mediated. In their review, Islam *et al.* [7] provide an update of the cellular, auto-immune and genetic factors known to play important roles in the generation of the thrombi. Current successful regimens are also outlined, along with potential emerging treatment strategies that may lead to a more optimal management of thrombotic APS patients via pathophysiology-based treatment strategies.

Shen and Huang [8] provide an insightful review focused on the potential repositioning of the old fungicide, ciclopirox (CPX) for new medical uses. CPX is considered a hydroxypyrimidine and has been used as a topical antifungal agent in various formulations (e.g., creams and shampoos) to treat superficial fungal infections for decades. Its effectiveness and safety have been demonstrated by multiple studies. Recently, CPX has been reported to inhibit tumor growth, mitigate diabetes and its complications, prevent human immunodeficiency virus infection, and improve age-associated cardiovascular defects. Interestingly, its antifungal activity and many of the newly observed effects are suggested to relate to its capability of chelating iron and interfering with the related signaling pathways. Shen and Huang [8] summarize the pharmacological and toxicological properties of CPX as an antifungal agent, the therapeutic potential of CPX for cancer and other human diseases, as well as the purported molecular mechanisms.

Alam *et al.* [9] describe the pathophysiological relationship between T2DM and Alzheimer's disease (AD) from a disease management perspective. Whereas T2DM and AD are two independent progressive disorders, evidence from epidemiological, pathophysiological and animal studies has indicated a close pathophysiological relationship linking them. Consequent to the pathophysiological overlaps between T2DM and AD, which includes the development of insulin resistance and deficiency, protein aggregation (amylin and amyloid- β peptides, respectively), oxidative stress, inflammation, autophagocytosis and advanced glycation end products - AD is sometimes referred to as "type 3 diabetes". In addition to the targeted regimens usually used for treating T2DM and AD individually; currently, anti-diabetic drugs are being evaluated to reduce the cognitive decline in AD patients. Therefore, in the event that a common pathophysiology of T2DM and AD could be clearly determined, the scenario would be supported that both disorders could potentially be managed more efficiently, possibly by shared pharmacotherapy, and evaluation of this would certainly aid the understanding of both diseases, and broaden the spectrum of preventive strategies to investigate. The aim of Alam *et al.* review [9] is to highlight pathophysiological overlaps that bridge T2DM and AD to lay a foundation for future treatment strategies for the management of both diseases.

Al-Saedi *et al.* [10] provide a systematic review focused on present challenges in the management of and future innovative trends to positively impact dry eye disease (DED). This tear film disorder results in hyperosmolarity of the tear film and inflammation of the ocular surface. DED is also referred to as keratoconjunctivitis sicca (KCS) and dry eye syndrome. DED represents a significant public health issue; indeed, it is the most common eye disorder and impacts 5 - 6% of the population. Its prevalence rises to up to 9.8% in postmenopausal women, and as high as 34% in the elderly; hence a greater understanding of the aetiological mechanisms that underpin this disorder is required. Despite the urgent need for safe and effective pharmacotherapies, there is currently only one approved medication, Restasis[®], to tackle DED. In their review article, Al-Saedi *et al.* [10] provide an overview of DED, its classification, epidemiology, pathophysiology, diagnosis, and risk factors. Special emphasis is placed on current treatment options for DED, such as artificial tears, lipid-containing lubricants, liposomal spray, inserts, anti-inflammatory or immunosuppressant drops, antibiotics, dietary omega-3 essential fatty acids, autologous serum, intense-pulsed-light (IPL), punctual plugs, moisture-retaining eyeglasses, hydrophilic bandage contact lenses and secretagogues. The review also summarizes new trends in DED treatment that are patented and are currently under investigation in clinical trials.

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 enthusiastically responded to our request by contributing to not only this and all three parts of the special issue of CPD [11-32]. We extend our appreciation to the peer reviewers for the time and expertise that each selflessly provided by revising individual contributions to a consistently high level of merit to allow completion of this Part C special issue of CPD. As a result of the combined efforts of this scientific team - remarkable for their extensive expertise across such a broad arena of diverse medical disorders and scientific technologies - the current special issue 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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