Published in final edited form as:

Curr Pharm Des. 2016 ; 22(20): 2923–2925.

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

Mohammad A. Kamal^{1,2} and Nigel H. Greig³

¹Metabolomics & Enzymology Unit, Fundamental and Applied Biology Group, King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia

²Enzymoics, 7 Peterlee Place, Hebersham, NSW 2770, Australia

³Drug Design & Development Section, Translational Gerontology Branch, Intramural Research Program, National, Institute on Aging, National Institutes of Health, Biomedical Research Center, 251 Bayview Boulevard, Baltimore, MD 21224, USA

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 to 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 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 B special issue of CPD, Islam *et al.* [1] review the role of natural products in relation to the management of thrombosis-associated disorders. Besides genetic influences, there are several acquired and environmental risk factors dominating thrombotic diseases. A considerable number of natural products showing antithrombotic activities (antiplatelet, anticoagulant and fibrinolytic) with no apparent or minimal adverse effects have been reported. In their article, several natural products used as antithrombotic agents that encompass medicinal plants, vegetables, fruits, spices and edible mushrooms have been recently discovered to impact key target sites (thrombogenic components, factors and thrombotic pathways), and are described. Importantly, the side effects, limitations and the

interactions of standard regimens with natural products are also discussed. The active components could underpin the basis for future research on antithrombotic drug development. As a future direction, more advanced research is warranted to support the characterization and development of potential natural antithrombotic medications to ensure their safe and efficacious use. Natural products have played a key and essential role in pharmaceutical research and development, as numerous current and past medicines (up to 60%) are either natural products or synthetic derivatives of them. This article provides an illustration as to the value of understanding and applying such knowledge.

Haque *et al.* [2] reveal and explore the current understanding of HSP90 as a novel therapeutic target for the treatment of cancer. HSP90, a ubiquitous molecular chaperone is considered as the most abundantly expressed protein in various human cancers, such as those of breast, lung, colon, prostate, leukemia and skin. The master regulator, HSP90 plays a pivotal role in the conformational stabilization, maturation and activity of its various labile oncogenic client proteins, such as p53, Akt, Cdk4, Cdk6, Raf-1 and v-Src in altered cells. Hence, securing and reliably applying knowledge to effectively inhibit such a master regulator for cancer therapy, appears to be a potential approach for combinatorial inhibition of numerous oncogenic signaling pathways simultaneously. Notably, considerable effort is being undertaken to characterize and develop novel molecular targets and inhibitors with the potential to block key signaling pathways involved in the process of tumorigenesis and metastasis. In this effort, HSP90 has acquired immense interest as a potent anticancer drug-target due to its key functional link with multiple signaling pathways involved in the process of cell proliferation and cell survival. Notably, geldanamycin and its derivatives are demonstrating encouraging results to inhibit HSP90 function in several cancers and, currently, some 17 drug candidates known to target HSP90 are being evaluated in clinical trials either as single agents or as a combinatorial therapy. Haque *et al.*, provide insights on novel drug target therapy by focusing on recent progress in understanding HSP90 chaperone structure–function relationships, the identification of new HSP90 client proteins and more importantly, on the advancements of HSP90 targeted therapy based on the various existing and emerging classical inhibitors. Such strategies provide a game plan of how other diseases could be approached.

Hassan *et al.* [3] report on the association of oxidative stress with psychiatric disorders. When concentrations of reactive species (both oxygen and nitrogen) exceed the antioxidative capability of an organism, the cells move to a state of oxidative impairment. The high risk of impaired membrane integrity, lipid and protein oxidation, protein mutilation, DNA damage and neuronal dysfunction are some of the fundamental consequences of oxidative stress. The authors provided a detailed table and supportive information indicating that oxidative stress is or can be associated with different psychological disorders. Different classical search terms, like “oxidative stress affective disorders”, “free radicals and neurodegenerative disorders”, “oxidative stress and psychological disorders”, “oxidative stress, free radicals and psychiatric disorders” and “association of oxidative stress” were employed in conjunction with each of the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic categories, of the American Psychiatric Association, and with the World Health Organization’s (WHO) International Statistical Classification of Diseases and Related Health Problems (ICD). Genetic, pharmacological, biochemical, case studies, clinical trials

and/or preclinical therapeutic studies were used to explore the molecular aspects of psychological disorders. In conclusion the multidimensional information supports the role of oxidative stress across assorted psychiatric disorders. The data not only provide detailed information about the involvement of oxidative stress in psychiatric disorders but also highlights new objectives for the development of therapeutic interventions.

In an intriguing review, Panahi *et al.* [4] shed light on the immunology of chronic obstructive pulmonary disease (COPD) and sulfur mustard-induced airway injuries for immunotherapeutic interventions. Sulfur mustard (SM)-induced airway injuries and COPD are distinguished by chronic inflammation of the respiratory tract, and share some commonalities regarding the cellular and molecular mechanisms that orchestrate airway destruction. As existing data regarding the immunobiology of COPD is much more available in contrast to SM-mediated injuries, and considering the parallels in the immunopathogenesis of these diseases, comparison of the immunopathogenesis of COPD and SM-induced respiratory complications may aid in both understanding and developing new treatment strategies for SM-induced injuries. The Panahi *et al.*, review outlines the role of different components of the immune system in the pathogenesis of COPD and mustard-induced respiratory complications, and supports a therapeutic basis for improving the management of the latter condition as the most common chronic complication of SM exposure.

Tran *et al.*, [5] underscore the importance that the development and application of nanoprecipitation technology has provided to the field of pharmacy. Over the last 3 decades, nanoparticle-based medicine has received tremendous attention as a basis from which potent and smart therapeutics can be potentially developed. As yet, few nanomedicine products have been approved for commercial use in the clinic, but examples exist such as Doxil (a doxorubicin encapsulated long-circulating liposome preparation) and Ambraxane (paclitaxel protein-bound particles for injectable suspension). However, the field of nanomedicine and its applications remain at a relatively early stage, and hence the preparation and use of nanoparticles has yet to reach its full promise. For the generation of nanoparticles of biologically important material, nanoprecipitation (NPT) can be induced by processes that further increase the supersaturation of the system, and include evaporation of the solvent, a reduction of temperature or by mixing with an anti-solvent. The NPT technique presents numerous advantages, in that it is a straightforward technique, rapid and easy to perform. In the Tran *et al.*, review, the process of NTP is described and discussed, and includes factors that influence the encapsulation efficiency, the nanoparticle size, the morphology and the stability of nanoparticle. The NTP process is considered a favourable one for preparing solid nanoprotein consequent to the mild conditions that support preservation of the required bioactivity of proteins. Whereas nanoparticle fabrication by this process has yet to reach the market, due to organic solvent and other issues, production equipment for large-scale manufacture is available to allow the application of this technology to keep moving forward to this important stage.

Bifari *et al.* [6] discuss current updates on cellulose acetate (CA) based nanocomposites for biomedical applications in their review. The development of polymer nanocomposites by incorporating variable nanofillers has attracted the attention of scientists, chemical engineers

and industrialists due to dramatic improvements in their various properties. CA based nanocomposites have an interesting history in the field of medical applications as CA meets a wide range of biomedical implant properties. Since CA is considered as a biodegradable, renewable, noncorrosive, non-toxic and biocompatible material, it has a number of unique advantages over many other materials. Bifari *et al.*, provide a broad overview of CA nanocomposites in the field of medical appliances and devices. This field has broad application and growing research suggests relevance across many scientific and medical specialties.

Bhattacharjee *et al.* [7] shed light on the formulation and application of biodegradable nanoparticle-based biopharmaceutical delivery. Biodegradable polymer-based drug delivery has emerged as a promising and successful clinical tool for specific targeting and controlled drug release delivery systems. The technology can be tailored to provide unique benefit for select agents to either overcome a pharmacokinetic/pharmacodynamic shortcoming associated with a different route or mechanism of administration, or to optimize a pharmacological advantage when targeting a particular condition such as by providing a prolonged, sustained circulation time, combined with biocompatibility and degradation to nontoxic by-products. To date, several biopharmaceutical agents have been successfully encapsulated within biodegradable polymers and effectively used in clinical medicine. However, before selection and clinical implementation of such nanocarriers, multiple different parameters should be considered that will ultimately influence the eventual success of different nanocarrier preparations, including their drug release profile, the size of nanocarrier, degradation mechanisms, toxicity profile, type of polymer used, appropriate synthesis method and selection of an optimal mode for their delivery. The Bhattacharjee *et al.* article focuses on such considerations to explore this important area of designing and developing biodegradable polymeric nanosystems that, when encapsulated with biopharmaceutical agents, can be safely and effectively applied across numerous drug classes for the treatment of broad number of diseases.

Alam *et al.* [8] provide an insightful review on the metabolic control of type 2 diabetes mellitus (T2DM) by targeting the glucose transporter 4 (GLUT4) as an intervention approach. T2DM is the most common form of diabetes, characterized by insulin resistance in the hepatic and peripheral tissues. GLUT4 plays a key role in the pathophysiology of T2DM. Its defective expression or translocation to the peripheral cell plasma membrane in T2DM patients hinders the appropriate cellular uptake of glucose for optimal energy production. In addition to suitable drugs, an appropriate diet and/or exercise can be implemented to target the increase in GLUT4 expression, GLUT4 concentrations and GLUT4 translocation to the cell surface when managing the glucose metabolism of T2DM patients. In their review, intervention strategies are discussed that were administered separately or coupled with diet and/or exercise aimed to potentially impact the expression and translocation of GLUT4 in T2DM after reducing the excess glucose load in the blood. Additionally, potentially promising synthetic and natural compounds, to activate the insulin-independent GLUT4 signaling pathways for the efficient management of T2DM, are highlighted as possible targets or emerging alternative sources for future drug development.

Kumar *et al.* [9] review the role of osmolytes in regulating the immune system. Key among numerous actions, the immune system has evolved to protect the host organism from a diverse range of pathogenic microbes that are, themselves, likewise constantly evolving. To achieve this, the immune system comprises a complex network of cells, humoral factors, chemokines and cytokines. Dysregulation of this immune system, at any of multiple levels can results in numerous kinds of immunological disorders. A number of external agents can influence control of immune function. Recent studies have revealed a role of osmolytes in the regulation of various immunological processes, which are systematically discussed and include antigen-antibody interaction, immunoglobulin assembly/folding/secretion, antigen presentation, regulation of immune cell function, inflammatory response and protection against photo-immunosuppression. Hence, osmolytes and their transporters can be considered as potential drug and drug targets, respectively, with future potential as a strategy to aid elucidate and treat various immunological disorders.

Ojha *et al.* [10] provide a systematic review focused on phytochemicals as archetypical pharmaceutical leads for drug development against diabetic cardiomyopathy (DCM). Phytochemicals can be described, in the strictest sense, as chemicals produced by plants that are not essential nutrients but often provide color, odor and flavor, and that may through a variety of mechanisms positively impact health. On a worldwide scale, type 2 diabetes mellitus (T2DM) is fast reaching epidemic proportions and poses major health care and socioeconomic challenges consequent to its numerous complications. Among these, T2DM is considered a major risk factor for the development of debilitating micro- as well as macro-vascular complications. Clinical studies have revealed that the development of DCM in diabetics occurs either dependent or independent of pre-existing increased risk factors, such as poor glycemic control, altered lipid profile and high blood pressure. As a consequence, DCM represents a major challenge to the clinical community in relation to both its efficient and early diagnosis as well as devising and instigating an effective treatment paradigm. Ancient traditional medical practices suggest that herbal extracts, containing phytochemicals, may be valuable in managing a broad range of ailments, including cardiac dysfunction, and are worthy of scientific evaluation under conditions where their purity, bioavailability, pharmacokinetics and other key factors impacting pharmacodynamics activity can be established and optimized for clinical use in humans. In recent years in DCM as well as other disorders, tremendous progress has been made to characterize the therapeutic action of phytochemicals and delineate mechanisms of action in pre-clinical disease models. In light of the lack of approved drugs available for the treatment of DCM, phytochemicals provide an interesting approach to fill a currently unmet medical need. The Ojha *et al.* article provides an update on such progress to understand cardioprotective mechanisms underpinning phytochemical actions, and potential caveats for their future pharmaceutical and clinical development.

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 this special issue of CPD. We additionally extend our gratitude to the peer reviewers for the time and expertise that each altruistically provided by revising individual contributions to a consistently high level

of distinction to allow completion of this Part B special issue of CPD. As a result of the united efforts of this scientific team - noteworthy for their extensive expertise across such a broad arena of diverse diseases and technologies - the current special issue provides to both the scientific and lay reader an important resource of reference for fast developing drug development strategies that possess substantial promise to benefit both medical researchers with interest in and, more importantly, those suffering from neurological, cardiovascular and metabolic disorders.

Biographies

Mohammad A. Kamal

Nigel H. Greig

References

1. Islam MA, Alam F, Khalil MI, Sasongko TH, Gan SH. Natural products towards the discovery of potential future antithrombotic drugs. *Curr Pharm Des.* 2016; 22(20):2926–46. [PubMed: 26951101]
2. Haque A, Alam Q, Alam MZ, et al. Current understanding of HSP90 as a novel therapeutic targets: an emerging approach for the treatment of cancer. *Curr Pharm Des.* 2016; 22(20):2947–59. [PubMed: 27013225]
3. Hassan W, Noreen H, Castro-Gomes V, Mohammadzai I, Rocha JBT, Landeira-Fernandez J. Association of Oxidative Stress with Psychiatric Disorders. *Curr Pharm Des.* 2016; 22(20):2960–74. [PubMed: 26951103]
4. Panahi Y, Jadidi-Niaragh F, Jamalkandi SA, et al. Immunology of chronic obstructive pulmonary disease and sulfur mustard-induced airway injuries: Implications for immunotherapeutic interventions. *Curr Pharm Des.* 2016; 22(20):2975–96. [PubMed: 26951100]
5. Tran TT-D, Tran PH-L, Tran V-T. Nanoprecipitation: preparation and application in the field of pharmacy. *Curr Pharm Des.* 2016; 22(20):2997–3006. [PubMed: 27055935]
6. Bifari EN, Khan SB, Alamry KA, Asiri AM, Akhtar K. Cellulose acetate based nanocomposites for biomedical applications: A review. *Curr Pharm Des.* 2016; 22(20):3007–19. [PubMed: 26979093]
7. Bhattacharjee S, Sarkar B, Sharma AR, et al. Formulation and application of biodegradable nanoparticles based biopharmaceutical delivery - an efficient delivery system. *Curr Pharm Des.* 2016; 22(20):3020–33. [PubMed: 26951099]

8. Alam F, Islam MA, Khalil MI, Gan SH. Metabolic Control of Type 2 Diabetes by Targeting the GLUT4 Glucose Transporter: Intervention Approaches. *Curr Pharm Des.* 2016; 22(20):3034–49. [PubMed: 26951104]
9. Kumar T, Yadav M, Singh LR. Role of osmolytes in regulating immune system. *Curr Pharm Des.* 2016; 22(20):3050–57. [PubMed: 26951102]
10. Ojha S, Kurdi A, Sadek B, et al. Phytochemicals as prototypes for pharmaceutical leads for drug development against diabetic cardiomyopathy. *Curr Pharm Des.* 2016; 22(20):3058–70. [PubMed: 27000825]