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Combination Therapy of Vascular Diseases and Fangjiomics: When West Meets East in the Era of Phenomics

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Combination drug therapy is now a common clinical practice in the treatment of complex vascular disease [1–5]. Different from monotherapy which uses a single drug that targets a pure molecule to treat a clinical condition, combination therapy uses a variety of drugs simultaneously to form a multi-drug regimen, usually a cocktail of several monotherapies that target at different molecules, to treat disease. Historically, combination therapy of vascular disease is designed by either empiric- or mechanism-based optimization of pharmacodynamics and pharmacokinetics for the purpose of improving drug efficacy and reducing toxicity or adverse reactions. However, combination drug therapy of vascular diseases is currently facing major challenges in terms of how to translate the knowledge of genomic research into clinical guidelines for the practice of personalized combination therapy of the phenotypically-complex vascular diseases [1–5]. On the other hand, multiple-target therapies of complex diseases, including vascular disorders, have been exploited for over 3000 years in Chinese medicine (CM). While these multi-target combination therapies with proven efficacy are mainly empiric-based, the underlying mechanisms remain mysteries [6–9]. In the era of post-genomics, the mega-scale data generation and integration of genomics, proteomics, metabolomics, and systems biology have not only advanced our understanding of the molecular basis of vascular biology, pathophysiology, and pharmacology but also highlighted the limitation of the conventional combination drug therapy in both CM and Western medicine and the urgent demand for new paradigm and approaches to develop genome-guided and personalized combination therapy of vascular disease [10, 11].

Fangjiomics a new emerging discipline developed from the CM focusing on design and evaluation of different combination therapy [8], seeks to systematically study myriad compatible combinations that may act through multiple targets and modes of action balancing between on-target and off-target. The development of *Fangjiomics* is based on 1) collecting diverse evidences of combination therapies from literatures; 2) revealing different

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mechanisms of combination therapies; 3) understanding dynamic characteristics of combination therapies; and 4) designing optimal pattern of combination therapies. By prioritizing targets, pathways and ingredient spectrum, *Fangjiomics* may lead to the discovery of controllable array-designed therapies to combine less potent elements with more on-target effects and fewer off-target effects than monotherapy. In many aspects, *Fangjiomics* addresses the key components and issues in treating vascular diseases with combination therapies, which may represent the next generation of strategies of clinical pharmacology and therapeutics for the personalized adequate treatment of complex disease [8, 12].

In this Special Issue of Current Vascular Pharmacology, we have assembled a series of articles of reviews, perspectives and original contributions from experts in current research of combination therapy of vascular disease. These articles summarize recent advances in phenomics of vascular disease [13], clinical *Zheng-hou* pharmacology [12], potential new targets for combination therapy including the volume-regulated Cl^- channels (VRCCs) and calcium-activated Cl^- channels (CaCCs) [14], microparticles (MPs) [15], adrenomedullin [16], and the endothelin-1 (ET-1) mediated ERK1/2 signaling pathways [17], and the application of CM and Chinese Patent Medicine (CPM) as new approaches to the treatment of cerebral [18] and coronary artery disease [19], hypertension [20] and diabetic complications [21, 22].

Selecting combination therapies based on different horizontal or vertical targets, such as the VRCCs and CaCCs [14], circulating MPs [15], and the ET-1-mediated ERK1/2 signaling pathways in hypertension-induced myocardial hypertrophic response [17], may be very promising in the treatment of variant vascular disease. The combination of CPM with routine anti angina therapy appears to be more effective in the treatment of angina pectoris than the routine treatment [23]. CM interventions of combination therapies to diabetic foot also displayed effectiveness [21]. The combination therapy could not only improve the quality of life and the symptoms of hypertensive patients, but also stabilize blood pressure variability based on systematic reviews (including meta-analyses) [19]. Besides, randomized controlled trials in the last decade demonstrated CPMs had the potential benefits in reducing the incidence of the endpoints and improving neurologic impairments, body movements, Barthel index, and quality of life. It is also noticed, however, that while most current literature indicated that the combination therapy of diabetic nephropathies with the angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARBs) plus effective CM drugs might have anti-proteinuric and renal protective effects, the clinical outcomes are not always consistent [22]. Clearly, newer strategies are needed for better rational design of combination therapy.

The phenomics strategy will allow the transition from focused genotype/phenotype studies to a global genome/phenome approach to the understanding of vascular diseases. The application of phenomics will identify a systemically integrated set of biomarkers for diagnosis and prognosis of vascular disease and provide treatment targets for combination therapy and thus make a significant paradigm shift in the clinical treatment of vascular diseases [13]. In the phenomic standpoint of view [13], *Zheng-hou* in CM can be regarded as an identifiable clinical phenome, which is the sum total of a patient's phenotypic traits

(*Zheng-hou*) that signify the expression of genome, proteome, and metabolome under specific environmental influence [12]. Accordingly, more attention should be directed to the translation of the diagnosis of a patient's *Zheng-hou* into the identification of dynamic variation of clinical phenome in our future clinical practice. Pharmacokinetics is becoming a useful approach to resolve the growing and complex issue of drug combinations to devise reasonable treatment regimens and to make physicians recognize the mechanisms of combined therapies [24]. In order to leverage breakthroughs in the genome-wide solutions for complex disease and drug responses through a combination of the current "omics" technology a new discipline in the modern translational Chinese medical science (CMS), the clinical *Zheng-hou* pharmacology (CZP), has been recently emerged [12]. It is hoped that CZP can help us better understand the clinical phenomics, including the disease phenome (*Zheng-hou*) and its response to the combination drug therapy (*Fangjiomics*) so that the personalized medicine with rational holistic diagnosis and individualized treatment can be finally achieved [12].

We believe that publication of this special issue will further promote international academic exchange and collaborations to accelerate understanding of mechanisms for human vascular disease and discovery of better designed regimens for personalized combination therapy of these devastating diseases.

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