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Editorial

Fangjiomics: revealing adaptive omics pharmacological mechanisms of the myriad combination therapies to achieve personalized medicine

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In Western medicine, therapeutic drugs for the treatment of diseases are required to have a well-defined pure molecular target (one protein or one gene) because the understanding of molecular mechanisms for diseases are largely based on the principle of phenotype-genotype relationship, *ie*, "one gene encoding one protein and responsible for one phenotype"[1]. In clinical practice, however, treatment of many diseases often requires a multi-drug regimen that combines several monotherapies targeting on different molecules to optimize pharmacodynamics and/or pharmacokinetics for the purpose of improving therapeutic efficacy and/or reducing toxicity and adverse reactions[2]. Recent findings from studies of pharmacogenomics and the newly-developed pharmacoproteomics[3] and pharmacometabolomics[4] have revealed pervasive effects of genetic polymorphisms on drug efficacy or toxicity, not only urging for personalized drug treatments according to individual patient's genetic characteristics but also adding more layers of complexity to the combination of multi-drug regimen[4]. Furthermore, the current definition of clinical phenotypes of disease (*eg*, hypertension, heart failure, type-2 diabetes, *etc*) and related drug therapy has shown serious limitations that conceal the ever-increasing details of genomic variants discovered by the genome-wide association studies (GWAs)[5]. Clearly, newer approaches are needed for Western medicine to refine the symptoms- or evidence-based definition of disease and drug responses so that the intrinsic complexity of the disease, the outcomes of drug treatment, and the impact of multiple environmental factors can be unequivocally characterized and classified. Obviously, this new approach for the redefinitions of disease and drug response (efficacy and toxicity) has to be at the "ome"-level to encompass a big range of symptomatic, morphological, biological, pathophysiological, behavioral, genomic, proteomic, and metabolomic features.

In the traditional Chinese medicine (TCM), fundamentally different from the Western medicine, diseased phenotypes are clustered as *Zheng-hou* and treated with a combination of several herbs called *Fangji*. While the empiric based *Fangji* therapy of *Zheng-hou* has been proven clinically effective, the underlying mechanisms for the combined targets remain mysteries.

Fangjiomics is recently emerged as a new discipline to systematically study myriad compatible combinations that may act through multiple targets and modes of actions balancing on-targets with off-targets[6]. Different mechanisms and dynamic characteristics of combination therapies are delineated through collecting diverse evidences and analyzing the designs of optimal patterns of *Fangji* therapy from the long history of clinical practice and literature. Fangjiome is composed of thousands of *Fangjis*. A variety of omics technologies and related analytical tools are combined to reveal the complex relationships in the Fanjiome at different omics levels. By prioritizing targets, pathways and ingredient spectra, 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.

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Based on archives of a *Fang-Zheng* Forum held in Beijing, China on November 24–25, 2013, we have assembled in this Special Issue a series of original research and review articles of Fangjiomic studies on several popular *Fangjis* in different sizes with diverse compositions of numbers of herbs or compounds. These papers represent some of the significant progress in Fangjimoics in recent years and its impact on not only TCM but also the application of systems biology, network pharmacology, and bioinformatics to the current translational medicine.

To rationally translate the studies of Fangjiomics into clinical practice, we should know clearly the relationship of multiple compounds and related effects. So a key concept of Fangjiomics is to highlight the effect-based compatibility principle of Chinese medicinal prescription (*Fangji*)[7] . In this regard, Li *et al* reviewed *Fangjis* of promoting blood circulation for removing blood stasis (PBCRBS) therapy for acute intracerebral hemorrhage patients. PBCRBS could ameliorate neurological function deficits, reduce volume of hematoma and volume of perihematomal edema, and lower mortality rate and dependency in comparison with Western conventional medication controls or placebo based on a Meta-analysis[8]. Wang *et al* summarized the recent investigations on the anticancer activities and possible molecular targets of the Compound Kusen Injection, and then hypothesized that altering gene regulation in several pathways including Wnt signaling pathway might be involved in the underlying mechanisms[9]. To summarize the targets distribution of *Fangjis*, Liu and Wang defined multiple modes of array-designed combination therapies of Fangjiomics, such as "magic shotguns", vertical, horizontal, focusing, siege and dynamic arrays according to hits on targets, pathways or networks[10].

Also included in this Special Issue are six original research articles that delineate the systematic and network approaches of Fangjiomics on several popular *Zheng-hous* or *Fangjis*, which are commonly used in TCM practice. A proteomic and metabolomic profiling of Kidney-Yin Deficiency Syndrome (KYDS) (*Zheng-hou*) patients with diabetes mellitus not only detected for the first time the potential biomarkers associated with KYDS, but also provided compelling evidence for the existence of a molecular basis in KYDS syndrome differentiation[11]. The network-based approach illustrated the complex therapeutic mechanisms of Xiao-Ke-An for type 2 diabetes through improving the carbohydrate and lipid metabolisms, ameliorating insulin resistance, attenuating diabetic vascular complications, and anti-inflammation[12]. Wang *et al* demonstrated that Chang'an II protected the intestinal mucosa against post-inflammation irritable bowel syndrome (PI-IBS) through integrated effects of immunomodulation, anti-inflammation, and anti-anxiety[13].

In two articles by Zhao *et al*[14] and Zhang *et al*[15] , the contributions of different parties in *Fangjis* to the total action of *Fangjis* were demonstrated. Though each single herb (Ramulus Cinnamomi, *Guizhi*; Paeonia lactiflora, *Shaoyao*; Rhizoma Anemarrhenae, *Zhimu*) could affect some diabetic peripheral neuropathy (DPN)-related functions and pathways, Guizhi-Shaoyao-Zhimu decoction showed more effects on those DPN-related functions and pathways, such as aryl hydrocarbon receptor signaling and apoptosis signaling[14]. A network analysis of the ingredients in Huanglian-Jie-du Decoction revealed their putative targets in ischemic stroke-related pathway systems[15]. With a rational combination of compounds diverse functions with different combined modes may emerge for the therapeutic purpose. For example, ursodeoxycholic acid and jasminoidin in the Qingkailing injection yielded ten new core pathways involving immune responses, apoptosis, and nervous system, *etc*. for the treatment of stroke and brain ischemia/reperfusion. This study provided new insight into the combination therapy of pure synergism[16].

Dose alterations result in variations of *Fangji*'s action. Guo *et al* demonstrated that overlapping and non-overlapping metabolites and metabolic pathways provided a dose-dependent metabolic mechanism for the neuroprotective effects of DanHong injection in the treatment of cerebral ischemia[17].

The composition of herbs *Fangjis* is different in size. The simplest *Fangji* has only a single herb or compound and is in the category of *Dan-fang*. Liu *et al* studied the effect of ginsenoside Rd on neurogenesis after focal cerebral ischemia/reperfusion injury (IRI) in rats and its underlying mechanisms. Even a single compound, Rd promoted neurogenesis after IRI by upregulating VEGF and BDNF expression through PI3K/Akt and ERK1/2 pathways[18]. Similarly, tannins fraction (PTFs) could induce apoptosis and inhibit the migration and invasion of NCI-H1703 cells via regulating the MMPs expression through MAPK/MMPs pathways in human lung squamous carcinoma cells[19].

These significant advances in application of the concepts and research approaches of *Fangjimocs* in the study of the adaptive regulation and hierarchical architectural theory of *Fangji*'s integrated and balanced paradigm of multiple targets, such as *Jun-Chen-Zuo-shi*, provide preliminary promise for Fangjiomics as a novel and effective approaches to the development of combination therapy in different diseases. In order to reveal the interconnections of multiple compounds, complex pathways and fluctuant networks of diseases and drug responses, we need to 1) understand how any alteration of *Fangjis* results in variations of *Zheng-hou* and drug response and treatment outcomes; and 2) reveal more and more pharmacological mechanisms of different *Fangjis* in the treatment of corresponding *Zheng-hou*.

In many aspects, Fangjiomics is in common with pharmacophenomics[20] in Western medicine. If we would define *Zheng-hou* as the disease phenome, Fangjiomics would provide clues and ideas for pharmacophenomics in identification of the corresponding therapeutic targets and drug responses. The translation of the knowledge of pharmacogenomics and pharmacophenomics *etc*. into clinical application of Fangjiomics would pave a new path to deconstructing the target networks and disease pathological pathways and help to understand the crosstalk of these pathways or sub-networks and to design optimal and perfect combination of multiple herbs or compounds that is effective to reverse those related pathways or

networks[21]. Therefore, we expect that the continuous application of Fangjiomics in the evaluation of more effective *Fangjis* on *Zheng-hou* may provide more solid basis for personalized medicine[22] in near future.

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