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Editorial

New omic and network paradigms for deep understanding of therapeutic mechanisms for Fangji of traditional Chinese medicine

Dayue Darrel DUAN[1, 2, *], Zhong WANG[3, *], Yong-yan WANG[3, *]

[1]*Center for Phenomics of Traditional Chinese Medicine/the Affiliated Hospital of Traditional Chinese Medicine, Southwest Medical University, Luzhou 646000, China;* [2]*Department of Pharmacology, University of Nevada Reno School of Medicine, Reno, NV 89557, USA;* [3]*Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China*

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Combination therapy with multi-drug regimen as an integrated intervention of several pharmacological compounds that interact with multiple targets, rather than monotherapy using a single compound that targets at a single molecule, is a common strategy for combating complex disease in both Western and traditional Chinese medicine (TCM)[1-3]. But each is based on different mechanistic principles. In Western medicine, a multi-drug regimen usually combines several monotherapies targeting on different molecules to optimize pharmacodynamics and/or pharmacokinetics to improve therapeutic efficacy and/or reduce toxicity and adverse reactions[1]. In TCM, the main therapeutics is the unique TCM medicinal formula, so called Fangji, which is usually composed of multiple herbs and medical materials with integrated multiple therapeutic objects. One of the major principles of Fangji compositions is Zhenghou based "Jun-Chen-Zuo-Shi" to orchestrate and integrate the multiple therapeutic targets for a specific Zhenghou[4]. The ingredients in a Fangji were thus composed according to the quaternity of Jun (monarch), which targets at the major etiological mechanisms, Chen (minister), which targets at the secondary etiological mechanisms, Zuo (assistant or associate), which targets at the associated factors to facilitate the therapeutic effects or reduce the adverse effects, and Shi (guide), which guides and orchestrates the targets[4]. Therefore, TCM Fangji combination therapy has embodied many principles of modern systems biology and omic theories[2, 3]. The therapeutic effects of TCM Fangji rely on the integrated whole function through compatibility of the drugs in the multi-drug regimen of Fangji[2]. For example, the Duhuo Jisheng Decoction (DHJSD) widely used in clinic for effectively combatting lower back pain (LBP) was developed with an integrated combination of 15-ingredients according to the principles of "Jun, Chen, Zuo, and Shi" to specifically target at the primary and secondary causatives of Bi Zheng[5]. It eliminates "feng-han-shi" and thus pain of "Bi Zheng" and promotes "Gan" and "Shen" function and therefore strengthens the bones and tendons, respectively. It also improves circulation and removes stasis of "Qi" and "Xue", reduces tissue swelling and relieves pain. Liu *et al* found that DHJSD inhibited the generation of proinflammatory factors and extracellular matrix (ECM) degradation of human intervertebral disc (HID) through an orchestrated targeting at multiple molecules in the SDF-1/CXCR4/NF-κB pathway, thus solved a puzzle of the quartanity of Jun-Chen-Zuo-Shi and added novel mechanistic insights into the clinical effectiveness of DHJSD on LBP[5]. Luo *et al* studied the Fangji of Yangxin Tongmai formula (YTF) in the treatment of pediatric Graves' disease (GD). They found that YTF enhanced glucose handling in GD children with impaired glucose tolerance through multiple targets to promote the bioactivity of insulin and to avoid the low density of insulin receptors that is induced by the feeble binding affinity of insulin[6].

The modern pharmacological approach to the study of Fangji, however, has been focusing on the isolation and identification of individual active components within a Fangji for cellular and molecular targets. Although this approach has led to the development of many new monomers purified from Fangji as new drugs widely used in clinical practice such as the antimalarial artemisinin[7], which has earned a Nobel Prize in Physiology or Medicine in 2015[8], the pharmacological bases of these purified effective monomers or active components have lost the TCM characteristics and are far different from the pharmacological theory and clinical applications of Fangji,

*To whom correspondence should be addressed.
E-mail dduan@medicine.nevada.edu (Dayue Darrel DUAN);
zhonw@sina.com (Zhong WANG);
wangyongyan2010@sina.cn (Yong-yan Wang)

in terms of the principles of combination therapy based on the composition theories such as the quaternity of Jun-Chen-Zuo-Shi. This not only has led to the misinterpretations of mechanisms of Fangji's therapeutic actions and clinical effectiveness but also has seriously hampered the scientific research and development of TCM in general.

Clearly, new omic/systematic and networking paradigms are urgently needed for deep understanding of the unique composition theories and mechanisms of effective combination therapy through TCM Fangji. Recent endeavors attributed to this revolutionary paradigm shift has resulted in the current special issue of Fangjiomics. Original studies and reviews on the application of genomics[9], transcriptomics[10], proteomics[10], metabolomics[11], fangjiomics[12, 13] and network pharmacology[12, 14] and network medicine[15-19] to the study of several classic Fangjis are incleded. The unbiased genome-wide association study (GWAS) and pharmacogenomics have been applied to dissect the genetic variants underlying complex diseases and individual responses to a given treatment[9]. Recent development of a full genetic model for analysis of gene-gene interactions (dominance and epistasis) and gene-environment interactions has substantially increased model power and remarkably improved the detection of association of GWAS and the construction of the molecular architecture[9]. This analysis can integrate other omic information and allow for variations of Fangji, which is very promising for Fangjiomic detection of the sophisticated molecular and structural architecture of the function of Fangji[9].

Zhang *et al* investigated the mechanisms of Guanxinjing capsules (GXJCs) on coronary heart disease (CHD) complicated with depression[14]. A total of 16 GXJC drug-like chemical constituents were identified by UHPLC-LTQ-Orbitrap assay and evaluation of oral bioavailability. Then, 870 genes were identified as the putative targets of these GXJC drug-like chemical constituents by using MedChem Studio. A CHD/depression therapeutic target network of GXJC was then constructed, and four topological features (degree, betweenness, closeness and K-coreness) were calculated. Based on the topological feature values of the GXJC putative targets, 14 main active constituents were identified. Their corresponding putative targets had topological importance in the GXJC putative target-known CHD/depression therapeutic target network, which were defined as the candidate targets of GXJC against CHD complicated with depression[14]. Functionally, these candidate targets were significantly involved in several CHD/depression-related pathways, including repairing pathological vascular changes, reducing platelet aggregation and inflammation, and affecting patient depression. Using this integrative pharmacology approach of active chemical constituent identification, drug target prediction and network analysis Zhang *et al* identified a list of main active constituents of GXJC acting on CHD complicated with depression. This approach to the identification and characterization of molecular targets of Fangji is more efficient and adequate than the conventional pharmacological approach and provides more accurate information for better understanding of the pharmacological mechanisms of TCM prescription of Fangji.

Fangjiomics, which was introduced in the previous special issue "Fangjiomics: revealing adaptive omics pharmacological mechanisms of the myriad combination therapies to achieve personalized medicine" in 2015[3], uses rational drug combinations with higher efficacy but fewer adverse effects in a controlled array of designs by systematically integrating diverse omics data on genomic, proteomic, and metabolomic interactions, in contrast to traditional "omics" techniques focusing on a certain level of cell, tissue, or organ[2]. Based on the integration of multi-scale omic data and quantitative modeling of the relationships between complex diseases and combination therapy, Fangjiomics-based combination therapy presents its feasibility to achieving precision medicine, which would ensure that patients receive the right treatment at the right dose and at the right time, with maximum efficacy and minimum side effects. In this special issue, we continued to introduce its applications to the discovery of rational combination therapy and precision medicine.

The emerging pharmacophenomics studies the orchestrated multi-target pharmacology of combination therapy and provides a systematical paradigm for the pharmacological study of Fangji[20]. With well-defined molecular mechanisms of Zhenghou at the level of multi-omics through phenome-wide association study (PheWAS) and a suite of new phenomics technologies and platforms, pharmacophenomics may be used to characterize the drug-response phenome of Fangji and to identify the corresponding multiple therapeutic targets according to the TCM theory of Jun-Chen-Zuo-Shi. Pharmacophenomic study of Fangji will also lay a theoretical foundation for the new science of precision medicine.

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