The Art and Science of Traditional Medicine
Part 1: TCM Today – A Case for Integration
In this first installment of a three part series, “The Art and Science of Traditional Medicine,” we present a series of articles making a case for the integration of traditional Chinese medicine (TCM) into modern medical practice. From the new WHO Traditional Medicine Strategy to the application of systems biology in studying TCM, we aim to highlight the potential for creating an integrated, network-based health care system. The next two issues will cover herbal genomics and highlight the importance of quality control, standardization, regulation, and safety for traditional therapies. An overview of indigenous medicines in Europe, Africa, the Middle East, India, and the Americas will also be provided.

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This is the start of something big.
Supporting the integration and modernization of traditional medicine

Nearly a quarter of all modern medicines are derived from natural products, many of which were first used in a traditional medicine context. Traditional medicine (TM) holds great potential to improve people’s health and wellness. It is often more affordable, more acceptable to people, and therefore also represent a tool to help achieve universal health coverage. It is commonly used in large parts of Africa, Asia, and Latin America. For many millions of people, often living in rural areas within developing countries, herbal medicines, traditional treatments, and traditional practitioners are the main—and sometimes the only—source of health care. The affordability of most traditional medicines makes them all the more attractive at a time of soaring health care costs and widespread austerity.

TM is often seen as more accessible, more affordable, and more acceptable to people and can therefore also represent a tool to help achieve universal health coverage. It is commonly used in large parts of Africa, Asia, and Latin America. For many millions of people, often living in rural areas within developing countries, herbal medicines, traditional treatments, and traditional practitioners are the main—and sometimes the only—source of health care. The affordability of most traditional medicines makes them all the more attractive at a time of soaring health care costs and widespread austerity.

In wealthy countries, TM meets an additional set of needs. People increasingly seek natural products and want to have more control over their health. They turn to TM to relieve common symptoms, improve their quality of life, and protect against illness and diseases in a holistic, nonspecialized way.

Incidentally, nearly a quarter of all modern medicines are derived from natural products, many of which were first used in a traditional medicine context. TM is thus a resource for primary health care, but also for innovation and discovery.

However, TM needs rigorous, scientific data to demonstrate its efficacy. It also needs evidence-based standards for quality and safety evaluation to support its appropriate regulation. I am happy to see included in this special feature of Science magazine, a series of perspectives on TM from a global team of experts, and would like to encourage more views to be shared and more robust research to be conducted in the area of TM in the future.

The general situation concerning the global use of TM was recently disseminated through the WHO Traditional Medicine Strategy 2014–2023. It makes clear that, to move into mainstream medicine on an equally trusted footing, TM needs a stronger evidence base. The need for stronger regulatory control covers not only the products, but also extends across the practice and practitioners. Updating and enhancing the strategy has allowed WHO to control covers not only the products, but also extends across the practice and practitioners. Updating and enhancing the strategy has allowed WHO to disseminate through the WHO Traditional Medicine Strategy 2014–2023.

A middle way for traditional medicine

Traditional medicine researchers are applying modern ‘omics and the latest technologies in an attempt to standardize traditional treatments.

I n discussions surrounding traditional healing techniques, a common perception is that those in the West most often take a reductionist approach to medicine, breaking down the body into ever-smaller parts in order to understand its inner workings. In the East, by contrast, medical practitioners are seen to take a more holistic view, regarding the body as a complex, integrated system and treating it as such. At some point in the past, these two philosophies were certainly at odds. However, this seems less so to be the case today. The line between Eastern and Western medicine is blurring as “alternative” healing practices such as acupuncture, meditation, and yoga have become popularized in the West, and as evidence-based science finds a foothold in the East, particularly in the realm of drug discovery and development.

The rise of systems biology as a discipline, starting around five decades ago but gaining sharply in acceptance and popularity in the last 20 years, has created a slow but unambiguous shift in the Western research paradigm. Reductionism, although still a respected philosophy, is no longer consistently the preeminent methodology of choice in biological research. Researchers around the world are coming around to the notion that, while we can learn much from understanding the finest details at a molecular level, particularly when it comes to treating disease, a deeper knowledge of the interactions between systems and networks is essential.

Conversely, taking a purely holistic approach can produce its own challenges. This is particularly true when quality control of medicinal products and reproducibility of results comes into question. No matter the weight of historical, anecdotal data, drug regulatory agencies such as the U.S. Food and Drug Administration (FDA) will not allow new therapeutics for human treatment without verifiable scientific evidence. Although there are many challenges inherent in meeting this requirement, traditional medicine researchers are applying modern ‘omics and the latest technologies in an attempt to standardize traditional treatments, especially through identification and isolation of bioactive compounds and careful analysis of their levels and activities in various herbal remedies.

In Buddhism, the Middle Way is described as the route to enlightenment—a path found by balancing opposing views, accepting neither extreme, but rather investigating both sides and finding a middle ground. Perhaps a Middle Way can be found for traditional medicine, one that takes the best of East and West and brings them together for the benefit of all.

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Margaret Chan, M.D.
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Integrating traditional medicine into modern health care

Almost every culture has its distinct herbal traditions, each with its indigenous plants and unique practices. But one premise unites them all—herbs have remarkable properties that make them a source of potentially powerful medicines.

Thanks to early explorers like Marco Polo (1254–1293), materia medica has been travelling between East and West for centuries. It is now important for us to harness the traditional medicines from across the globe. In Britain, the rich history of traditional medicine use was given credibility in the early 1500s by the Herbalists Charter of Henry the VIII (1491–1547). His contemporary in China, Li Shihzin (1518–1593) was a great naturalist who spearheaded a 400-year research project that led to the publication of Bencao Gang Mu, a pharmacopoeia and also a treatise on botany, zoology, mineralogy, and metallurgy.

To make the case that traditional medicine has valuable insights for modern society, an independent editorial team was gathered consisting of experts in a range of topics related to traditional medicine research. This team compiled a unique collection of state-of-the-art perspectives from global experts on traditional medicine research, the first installment of which is presented in this special feature. Further exciting articles will be published early in 2015. We have chosen traditional Chinese medicine (TCM) to illustrate the art and science behind the ancient practice of holistic healing, and how the cannot be achieved by modern medicine alone. The personalized approach of Chinese medicine theory and modern omics technologies and practices of quality control, pharmacology and toxicology testing, carefully designed clinical studies, and proper regulation are applicable to all traditional medicines.

This first issue introduces the WHO Traditional Medicine Strategy (2014–2023), highlighting the global scientific challenges and showing how a systems biology approach can be applied to diagnosis, leading to integrated network-based medicine. Recent advances in mechanistic studies of acupuncturism are also discussed. Some of the exciting areas in TCM research include the therapeutic potential of herbal remedies against influenza, cancer, diabetes, and cardiovascular diseases; the exploration of gut microbiota-targeted dietary interventions against chronic inflammation; and the study of the biological activities of complex polyphenolic plant material.

A better understanding of the philosophy of synergetic interactions of Jun, Shi, and Shi classes of Chinese materia medica used in traditional formulations has led to a simplified Jun-Shi compatibility drug discovery strategy model. Chemogenomics and network pharmacology have been applied to predict molecular targets and decipher the mechanisms of action of pure compounds or phytocomplexes found in combinatorial herbal formulas. A better understanding of the safety of herbal medicines is critical to their wider acceptance as valid therapeutic agents. Integrated toxicological approaches have been successfully applied in this area, for instance to identify antifibrotic and pro-fibrotic substances in certain medicinal plants. As research into the broader application of traditional medicine continues, newer ‘omics technologies and poly-phenomancetixs will also play an increasing role in bridging the gap between the personalized approach of Chinese medicine theory and modern clinical research methodology.

Acknowledgments

We are particularly grateful to Zhu Chen, vice-chairman of the Standing Committee of the National People’s Congress of the People’s Republic of China for inviting us to undertake this project, to WHO Director-General Margaret Chan and her team, Commissioner Guojiao Wang of the State Administration of Traditional Chinese Medicine, and AAAS CEO Alan Leshner for their vision and support for this special feature.

The WHO Traditional Medicine Strategy 2014–2023: A perspective

The WHO Traditional Medicine Strategy 2014–2023: A perspective

here has been a continuing demand for, and popular use of, traditional and complementary medicine (T&CM) worldwide. In some developing countries, native healers remain the sole or main health providers for millions of people living in rural areas. For instance, the ratio of traditional health practitioners to citizens in Africa is 1:500, whereas the ratio of medical doctors to citizens is 1:40,000 (1). In the Lao People’s Democratic Republic, 80% of the population live in rural areas, with each village being serviced by one or two traditional health practitioners (2). Over 100 million Europeans are currently users of T&CM, with one-fifth being regular users; a similar level of acceptance and practice of herbal health care that includes T&CM (3). According to a national survey in China, practitioners of traditional Chinese medicine inpatients was 13.6 million, or 16% of the total in all hospitals surveyed (4). In a few countries, certain types of traditional medicine (TM) have been completely integrated into the health care system, including China, the Democratic People’s Republic of Korea (North Korea), the Republic of Korea (South Korea), India, and Vietnam. In China, for instance, traditional Chinese medicine and conventional medicine are practiced alongside each other at every level of the health care service, and public and private insurance cover both forms of treatment (Box 1).

In many other countries, T&CM is partially integrated into the health care system, while in some countries there is no integration at all.

Recent changes, emerging challenges, and needs

Much has changed since the last World Health Organization (WHO) global strategy document was released in 2002. More and more countries are coming to accept the contribution that T&CM can make to the health and well-being of individuals and communities, and to the overall health care systems. In the period 1999 to 2012, the number of member states of WHO with national policies covering TM has increased significantly. This includes countries better regulating herbal medicines or creating national research institutes to study T&CM (5).

Governments and consumers are becoming more open to broader use of T&CM practices and products and practitioners as an integrated part of health service delivery. In Africa, the number of national regulatory frameworks increased from one in 1999 to 2008 to 28 in 2010 (6). Across the Atlantic, the Ministry of Health in Brazil has developed a national policy on integrative and complementary practices (7), while in the eastern Mediterranean region, five member states report having reg-

ulations specifically for T&CM practitioners (5). Member states in the southeast Asia region are now pursuing a harmonized approach to education, practice, research, documentation, and regulation of TM (5). In Japan, 84% of Japanese physicians use T&CM in their practice, and there are many TCM practitioners in the USA (8). In Switzerland, certain complementary therapies have been reinstated into the basic health insurance scheme available to all Swiss citizens (9).

Despite significant advances, the regulation of T&M products, practices, and practitioners is not occurring at an equal pace (5). Member states report that faster progress is being made in the regulation of herbal medicines, while that for T&M practitioners and practitioners is lagging. Of concern is that the safety, quality, and efficacy of T&M cannot be assured if there is not appropriate regulation of products and practitioners. This situation provides a unique opportunity for many member states, where a lack of knowledge and experience exists regarding the formulation of national policy, leading to lack of national regulations and a lack of proper integration of T&M services into the health service delivery system. It also reflects the need of all member states to push WHO to update its global strategy on TM.

The WHO Traditional Medicine Strategy 2014–2023

Responding to the needs and challenges identified by member states and building on the work done under the WHO Traditional Medicine Strategy 2002–2005 (10), the updated strategy for the period 2014–2023 devotes more attention than its predecessor to health services and systems, including T&CM products, practices, and practitioners. The objectives of the updated strategy are summarized below.

Objective 1: To build the knowledge base for active management of T&M through appropriate policies, interventions, and tools.

This includes a diverse range of approaches, including measures that contribute to the safety, quality, and efficacy of T&M services and products, as well as tools to promote and facilitate the sharing of good T&M practice both nationally and internationally. This includes the development of quality standards for T&M products and services, and support for the development of systems to facilitate the registration and approval of T&M products and practitioners.

Objective 2: To strengthen quality assurance, safety, proper use, and effectiveness of T&M by regulating T&M products, practices, and practitioners.

This includes the development of quality standards for T&M products and services, and support for the development of systems to facilitate the registration and approval of T&M products and practitioners.

Objective 3: To support integration of T&M into the health and healthcare systems.

This includes the development of quality standards for T&M products and services, and support for the development of systems to facilitate the registration and approval of T&M products and practitioners.

Objective 4: To support the development of T&M education, research, and documentation.

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BOX 1. Traditional medicine health service integration in China.

In China, there are about 440,700 health care institutions providing TM services, with 520,600 patient beds, including all levels of TM hospitals and general hospitals, clinics, and health stations in urban and rural areas. About 90% of general hospitals include a TM department and provide TM services for all patients. TM medical institutions are governed by the same national legislation as conventional medical institutions. TM practitioners are allowed to practice in public and private clinics and hospitals. The public is free to choose the TM form of health care services, or follow the advice of their doctors (12).

One of the most significant questions raised about T&CM in recent years is how it might contribute to universal health coverage by improving service delivery in the health system, particularly primary health care. A first step is to capitalize on the potential of T&CM to improve health services and health outcomes. Mindful of the traditions and customs of peoples of every country, member states should consider how T&CM might support disease prevention or treatment as well as health maintenance and health promotion. This process should have safety, quality, and effectiveness standards and in line with patient choice and expectations. Based on each country’s realities, it is recommended that integrating T&CM into national health systems should be explored.

Next, it is important to ensure that consumers of T&CM can make informed choices about self-care health. In many member states, self-selection of T&CM products accounts for a large proportion of drug consumption, but members states together with ethical and legal considerations, should support and shape the key aspects of informed choice for T&CM intervention.

The WHO resolution WHA67.18 urges member states to adapt, adopt, and implement the WHO Traditional Medicine Strategy 2014–2023, to support T&CM programs or work plans and to report to WHO on progress in implementing the strategy. The resolution also encourages WHO to support member states’ implementation of the strategy in the coming decade (11).

Conclusions

Around the world, T&CM continues to grow in popularity. Progress in the regulatory gaining momentum, even as that of T&CM practices and practitioners advances at a somewhat slower pace. Safety, quality, and effectiveness of T&CM services is paramount, but cannot be ensured if appropriate regulations of practice and practitioners is not in place. The goals of WHO Traditional Medicine Strategy 2014–2023 are to support member states in harnessing the potential contributions of T&CM to health, wellness, people-centred health care, and health systems and general hospitals cover-

age, while also promoting safe and effective use of TM products and integration of TM products, practices, and practitioners into the health system, as appropriate. It should be emphasized that given the diverse nature of products, practitioners, and T&CM in each member state, it is important to enhance international communication and collaboration in sharing knowledge and practices, in developing and exchanging scientific knowledge and Ayurvedic medicine, and in sharing experiences in developing research and implement regulations. Also, as the marketplace for T&CM becomes more globalized, the quality, safety, proper use, and efficacy of T&CM in different nations need to be harmonized and standardized utilizing evidence-based science.

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ative bromelain from plants to synthesize a wide range of small molecules of great

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acupuncture was compared to no acupuncture (in effect, no medication an acceptable form of treatment? This is still, for many Western practitioners, a quandary to which there is no answer). Is a contextual effect (some would call it a placebo) that relieves pain and reduces the need for analgesics and counter-irritants? Understanding this ancient tradition is a good place to turn for insights that will improve pain treatment.

**FIGURE 2. Acupuncture effects compared with controls.** The results of a meta-analysis of 29 high-quality randomized controlled trials of acupuncture are shown for three conditions. Differences in the average standardized mean (with 95% confidence intervals) for treatment relative to control is shown. When compared to no treatment, acupuncture produces striking improvement; however, when compared to sham treatments, the effect is more modest (5).

**A:** Artemisia annua, also known as sweet wormwood or qinghao. (B) The chemical structure of artemisinin.

**TABLE 2.** Acupuncture effects compared with controls. The results of a meta-analysis of 29 high-quality randomized controlled trials of acupuncture are shown for three conditions. Differences in the average standardized mean (with 95% confidence intervals) for treatment relative to control is shown. When compared to no treatment, acupuncture produces striking improvement; however, when compared to sham treatments, the effect is more modest (5).

**FIGURE 2.** Acupuncture appears to modulate the central circuitry for pain (6), partially from the peripheral actions of endorphins (7) and partially from the centralization of endorphins (8). Moreover, there may be overlap in the descending pain circuits recruited by the specific and contextual effects. Ultimately, the goal of the research is clear: We need better treatments for pain without the sedative, narcotic, and addictive effects of the available drugs. Understanding this ancient tradition is a good place to turn for insights that will improve pain treatment.

**Traditional versus modern medical systems**

A major difference between resource intensive and resource poor environments is the extent to which common complaints of daily living are viewed as medical problems requiring intervention, help, and treatment. Medicalization has been defined as, “the process by which human conditions and problems come to be defined and treated as medical conditions, and thus become the subject of medical study, diagnosis, or treatment” (9). As health care providers in resource-intensive environments, we often take for granted the medicalization of a whole range of complaints—sadness, worry, fatigue, musculoskeletal discomforts, and even restless legs—as necessary and normal. Comparisons of traditional and modern health systems challenge these assumptions. Modern medicine has created a set of symptoms-based diagnostic categories for a range of common problems that differ greatly from those in traditional health systems. Diagnostic criteria, based on symptoms and limited physical findings but lacking laboratory diagnostic criteria, have been developed for a variety of physical conditions, such as chronic fatigue syndrome and chronic functional pain syndromes such as fibromyalgia, interstitial cystitis, vulvodynia, and chronic prostatitis. These diagnostic categories carry clinical insights about symptoms that cluster together, and sometimes patients can benefit. The diagnoses may provide some clarity and community support. Nevertheless, although there is some evidence for efficacy of pharmaceutical treatments for some such conditions, often these disorders respond inconsistently or poorly to available treatments. There is also clinical concern that sometimes these diagnoses contribute to an expectation of chronic functional impairment.

Traditional diagnoses often emphasize a temporary imbalance and promote an expectation that the subject will return to health. Although many patients with these conditions seek alternative remedies, most of the evidence of benefit is anecdotal. In resource-poor environments, people almost certainly suffer from the same set of symptoms, and at least, these complaints may sometimes be effectively addressed through the care of traditional healers. We are currently supporting a small number of trials that address whether the emotional and social support of interventions such as tai chi (70), yoga, or mindfulness-based meditation may capture some of the benefits of the healing traditions. Clearly, Western medicine does not have all the answers, and systems of care that allow thoughtful integration of healing traditions with modern medicine may offer help to troubled patients.

**References**

East is East and West is West, and never the twain shall meet? 

Theorizations from a variety of disciplines, developing an expanded view of medicine. Systems thinking, and in particular systems biology, have been recognized as the scientific bridge between Western medicine and traditional medicine models, including traditional Chinese medicine (TCM) [2, 3]. Figure 1 illustrates how systems-based theories can bridge Eastern and Western models, as it connecting ancient and modern ideas. The left forward image shows a dynamic correlation network of interactions between various genes, proteins, and metabolites. This nodal network reflects the particularized understanding of the complexity of biochemical pathways and the dynamic organization of the body that characterizes Western biology. The right forward image is a drawing of the Taoist Inner Landscape. In keeping with ancient Taoist tradition, the drawing provides a poetic description of the complex relationships among the various organs functions of the body. The background of the figure merges two very different physical systems: the laws of nature arose in Eastern cultures, such as China. Although there are many similarities between the Greek and Chinese systems of thought, the left side of the figure shows a simplified, hierarchical view of molecules being organized into cells, with further consolidation into tissues, organs, and, ultimately, a whole organism. This includes the bottom-up approach practiced in Western biomedical sciences. Knowledge of knowledge about the dynamic relationships among signs and symptoms. The Taiji (often called the Yin-Yang symbol in the West) represents the Eastern, Taoist tradition of systems thinking. It depicts a dynamic relationship between the two components of a duality that encompasses the known universe. Interestingly, the Taiji, which symbolizes humanity as part of an eternal universe, has all the properties of a fractal.

Amalgamation in action

Figure 2 depicts an amalgamation of Western and Eastern medical systems to the left side of the figure shows a simplified, hierarchical view of molecules being organized into cells, with further consolidation into tissues, organs, and, ultimately, a whole organism. This includes the bottom-up approach practiced in Western biomedical sciences. Knowledge of knowledge about the dynamic relationships among signs and symptoms. TCM concepts have a basis in actual biological variation and renal function. Several other studies have also shown that biological and clinical knowledge about the dynamic relationships among signs and symptoms. The path ahead

In the above studies, TCM subtyping and Western diagnostic criteria. This suggests that symptom patterns among patients with pre-diabetes should be used to standardize the segregation of patients into TCM subgroups [15]. The comprehensive symptom questionnaire used in the RA study was based on the TCM perspective of the Cold.

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Zheng: A systems biology approach to diagnosis and treatments

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Traditional Chinese medicine (TCM) is an ancient medical practice system which emphasizes regulating the integrity of the human body and its interactions with natural environments. As a key concept in TCM, Zheng (meaning syndrome or pattern) is the overall physiological and/or pathological pattern of the human body in response to a given internal and external condition, which usually is an abstraction of internal disharmony defined by a comprehensive analysis of the clinical symptoms and signs gathered by a practitioner using inspection, auscultation, olfaction, interrogation, and palpation of the pulses (1). Correctly identifying the Zheng is fundamental for the diagnosis and treatment of diseases.

Moreover, Zheng has been historically applied as the key pathological principle guiding the prescription of herbal formulas (Figure 1). A lack of research on Zheng has left us with little understanding of its underlying biology or the relationships between different Zhengs, diseases, and drugs. Moreover, there have been attempts to integrate Zheng differentiation with modern biomedical diagnostic methods, though these efforts have not achieved the desired results (2). Many well-known traditional recipes, such as Liu Wei Di Huang Wan and Jin Gui Shen Qi Wan, have long been used for the clinic treatment of Zheng disorders; however, Zheng-guided treatments are still scarce due to the lack of evidence-based interpretations of syndromes and treatment efficacies. Thus, investigating the biological basis of Zhengs from a molecular level is fundamental for the diagnosis and treatment of diseases.

Intriguingly, Zhengs are perceived as wholly distinct paradigms today, they provide insights into regulatory coherence at a high systems level (18, 19). Indeed, these coherent light functions may be directly involved in communication in addition to influencing biochemical networks (20, 21). It should also be clear that modern quantitative technologies developed in the West have a great deal to offer to Chinese diagnostics. Especially relevant are methodologies that provide information about the large-scale organization of systems as well as the dynamic of such organization (Figure 2). Integration of Western and Chinese medicine thinking has enormous potential for synthesizing modern technological systems as well as the dynamics of such organization (Figure 2).

Figure 2. Systems medicine. A hierarchical systems view on human biology (left) – scientific studies in Western medicine develop typically via a biochemistry/pathway bottom-up approach, while in Chinese medicine, a top-down dynamic symptom relationship approach is used (right). The right image illustrates the diagnostic bridge between symptom relations in Chinese Medicine bi-syndrome (top) and Western medicine (bottom) for rheumatoid arthritis.

Zheng-guided disease research

In Western medicine, a disease is a particular abnormal and pathological condition that affects part or all of the human body and is often construed as a medical condition associated with specific symptoms. By contrast, Zheng puts forth a very different definition of a disease and encompasses all of the symptoms a patient presents. Because of the highly interconnected nature of the human interaction networks, it is often the case that symptoms at the molecular level completely independent of one another (3), and this issue also applies to Zhengs. Moreover, Zhengs are dynamic with changing boundaries, overlapping symptoms, and a multiscale nature, which makes them difficult to understand at a biological and mechanistic level. Thus, we propose that a comprehensive Zheng map be constructed that links together all the Zhengs based on their molecular and cellular relationships. Further, we suggest creating the “Zhengome” as a new ‘omics field, in which a network is the basic research unit used to investigate the hierarchy present in the human body, from the molecular to the systems level. A comprehensive understanding of the Zhengome requires us to bring together multiple sources of evidence, from shared genes to protein-protein interactions, shared environmental factors, common treatments, and phenotypic and clinical manifestations, in order to capture the relationships between the different Zhengs.

Zheng uses the Yin-Yang, exterior-interior, cold-heat, and deficiency-excess definitions to describe clinical conditions, which are then managed by Zheng-specific recipes (Figure 1). Modern ‘omics techniques combined with bioinformatics and bioweb network models through a systems biology approach have

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Acknowledgments
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FIGURE 1. Using systems pharmacology and systems biology approaches for understanding TCM Zheng can help bridge the gap between herbal medicines and diseases. So, face color: Xing, body shape: She, tongue texture: Mai, pulse.

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intriguing area being examined is the coherent, spontaneous ultra-weak photon emission patterns of organisms (16, 17). Recent work suggests that photon distribution dynamics may provide insights into regulatory coherence at a high systems level (18, 19). Indeed, these coherent light functions may be directly involved in communication in addition to influencing biochemical networks (20, 21). It should also be clear that modern quantitative technologies developed in the West have a great deal to offer to Chinese diagnostics. Especially relevant are methodologies that provide information about the large-scale organization of systems as well as the dynamic of such organization (Figure 2).

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FIGURE 2. Systems medicine. A hierarchical systems view on human biology (left) – scientific studies in Western medicine develop typically via a biochemistry/pathway bottom-up approach, while in Chinese medicine, a top-down dynamic symptom relationship approach is used (right). The right image illustrates the diagnostic bridge between symptom relations in Chinese Medicine bi-syndrome (top) and Western medicine (bottom) for rheumatoid arthritis.

been applied to investigate the differences between Zhengs and to identify novel biomarkers. For instance, rheumatoid arthritis (RA) patients differentiated on the basis of “hot” and “cold” Zhengs have been shown to be associated with different underlying genomic and metabolic profiles, with the RA hot group showing more apoptotic activity than the cold group (6). Additionally, Li et al. used a network-based computational model to understand Zheng in the context of the neuro-endocrine-immune network and found that cold and hot Zhengs were closely related to a metabolism-immune imbalance (5). Wang and colleagues investigated the urine metabolome of patients with disease syndrome and its two subtypes of Yang Huang (acute) and Yin Huang (chronic), and identified several biomarker metabolites (6). However, most of the current studies have relied on only one or two approaches for molecular profiling and have lacked an efficient method to integrate data obtained at different ‘omics’ levels. These studies also did not look at combining the analysis of molecular data with clinical variables, possibly missing an opportunity to generate more convincing conclusions. Considering the limitations of past studies, future efforts should integrate an analysis for all levels of ‘omics’ (e.g., genomics, transcriptomics, epigenomics, and proteomics) data from a large number of patient samples for different Zhengs and include an investigation of the prognostic and therapeutic utilities of the data as a whole. Combining these molecular data with patients’ clinical information could provide evidence-based theoretical interpretations for Zhengs and enable an assessment of the Zheng-based therapeutic approaches.

Zhengs may change dynamically during disease progression. Differentiating the specific Zheng involved in each stage of a disease could provide valuable guidance for prescribing a dynamic therapeutic strategy. Using dynamic network modeling, a disease process can be conceptualized as spatio-temporal changes in network structures. The changes associated with a Zheng under dynamic therapy can be used to identify the key factors in the dynamic biological networks. Appropriate network perturbation models and subsequent robustness and stability analyses could help unveil potential disease-related genes or therapeutic targets involved in a disease’s progression or evolution (7). The relationships between the different aspects of a disease (e.g., main symptoms versus complications) in a specific Zheng, as well as the psychological, social, and even environmental factors should be taken into account during the modeling and simulation process in order to uncover the dynamic nature of complex diseases. Combining a Zhengome approach with dynamic modeling has the potential for establishing an accurate and quantitative Zheng research model, as well as for creating a new system for performing disease research.

Zheng-driven drug discovery

Despite considerable progress in genome, transcriptome, proteome, and metabolite profiling and throughout screen- ing methods and in rational drug design, drug discovery often encounters considerable costly failures that challenge the feasibility of the pipeline of drug discovery. Zheng-driven drug discovery has shown tremendous success for traditional drug discovery throughout Chinese medicine’s history. However, since this concept is completely new to Western medicine, it is no easy task to incorporate Zheng-driven drug discovery into modern drug discovery workflows. Here, we propose the “Zheng to TCM” and “TCM to Zheng” strategies within the framework of systems pharmacology to investigate biological systems and develop new therapeutics (Figure 2). The first strategy, Zheng to TCM, proposes developing a pipeline from Zheng diagnoses to TCM drugs, including differentiating Zhings, identifying Zheng-related diseases and the associated genes and proteins, reverse targeting of drug effects, constructing and analyzing network/systems, and finally identifying effective herbal medicines (8). In effect, this strategy can be considered a reverse targeting and screening approach that is designed to uncover drugs from natural products that can target multiple Zhings or related diseases. The goal of this method is to help researchers identify the active components within medicinal plants and multi-ingredient synergistic herbal formulas or drug combinations (9). In fact, this novel strategy has already been successfully applied in a qi-blood study, where we identified the active compounds in the qi-enriching and blood-tonifying herbs, their targets, and the corresponding pathways involved in the treatment of qi and blood deficiency syndromes (8).

The second strategy, TCM to Zheng, consists of a whole-system evaluation process starting with herbs or herbal formulas and culminating in identifying the Zheng. This process includes the initial collection and classification of herbal medicines, screening the ingredients for absorption, distribution, metabolism, excretion, and toxicity (ADME/T); performing targeted drug screenings and tissue localization; constructing and analyzing networks; and finally identifying Zheng/diseases (10). Using this strategy, it is possible to identify novel multitarget drugs in natural products (11). One particularly striking example is the systematic analysis of blood stasis and qi deficiency syndrome in coronary heart disease and the herbal drugs used to treat the syndromes. The results indicate that the herbs for eliminating stasis have pharmacological activity that acts to dilate blood vessel, improve the microcirculation, reduce blood viscosity, and regulate blood lipid, while qi-enhancing herbs help to improve the potential for enhancing energy metabolism and anti-inflammatory activity (12). The TCM to Zheng strategy can also help to elucidate the pharmacological effectiveness of herbal medicines.

In our ongoing work investigating Pi-deficiency syndrome (PDS) in the context of Zheng, we are analyzing patient samples using the sequencing alternative polyadenylation sites (SAPAS) method, RNA sequencing (13), lipid metabolomics, proteomics, and transcriptomics in order to decipher the pathogenesis and complex responses of the human body to PDS. From a drug development perspective, we plan to systematically investigate the Si Jun Zi decoction, a widely used herbal recipe for PDS, within the framework of the “TCM to Zheng” strategy, so as to understand why this recipe can regulate the immune response, stimulate blood circulation, and adjust gastrointestinal digestive functions. Despite the progress in Zheng-guided drug discovery, its future success requires the integration of multidisciplinary technologies, together with fertile innovations in the fields, to facilitate the understanding of multifactorial diseases and the development of new therapies.

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Integrated network-based medicine: The role of traditional Chinese medicine in developing a new generation of medicine

According to the philosophy of traditional Chinese medicine (TCM), health is the state of harmony between individual internal physiological networks (IPNs) and external environmental networks (EENs). Aberrant interactions between and within these networks cause complex diseases. TCM is grounded in these holistic principles, integrating philosophies from art and science; it stresses the maintenance of balance, or homeostasis, between the systems of the body and nature.

We believe that this kind of network-based holistic approach to medicine offers a useful counterpoint to today’s biological reductionism-based thinking. We champion integrated network-based medicine (INBM) which takes a systems approach to understanding the individual’s body as a whole, as opposed to relying on discrete components such as gene mutations, in order to explain illness (1). Built on the principles of IPNs and EENs, INBM offers a comprehensive medical system that integrates fundamental theories, diagnostic methods, and therapeutics based on a holistic and dynamic network-based approach.

The INBM system

Reductionist approaches to medicine, such as phenotype-based and target-based biomedicine (TBBM), are limited by their failure to consider the interactive nature of the human body and its environment. TBBM often views a disease as a tissue/organ-based condition that presents a single target for treatment, such as the elimination of a pathogen or the tissue/organ-based condition that presents a single target for treatment. For example, metformin was originally regarded solely as an anti-diabetic drug that inhibits the mitochondrial respiratory chain and activates the 5’ adenosine monophosphate-activated protein kinase pathway, resulting in inhibition of gluconeogenesis and the lowering blood glucose levels (2). Recently, a novel anti-cancer effect of metformin was identified by studying the overall impact of drug on the glucose metabolic network (3). This has raised the possibility that the drug will have new therapeutic uses (4). Efforts to focus on a single target can also have deleterious effects on the body’s overall system. An example is indomethacin, a conventional Western-medicine drug. Indomethacin exerts an anti-inflammatory effect by inhibiting prostaglandin E2 (PGE2) synthesis (5), but this suppression of PGE2 also affects a receptor for mucus secretion, leading to gastric mucosa damage (6, 7). A holistic view of the body’s network of connections will anticipate such positive and negative impacts of medical treatments.

INBM requires rigorous conceptual design and practical implementation, and TCM has many principles and resources to help achieve this. These include “pattern differentiation in diagnosis and treatment of diseases,” which can be regarded as a basic principle for individualized INBM (8). The “three m’s” of Chinese herbal medicine (CHM) provides another example: these are “multi-chemical components,” “multi-pharmacological effects,” and “multi-action targets and pathways.” The complex herbal formulae of CHM are intended to holistically modulate a person’s physiological/pathological networks and, in developing new drug combinations, the “three m’s” offer a useful optimization tool (9).

Figure 1 illustrates how the “three m’s” approach to the

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FIGURE 1. How integrated network-based medicine (INBM) works. TCM, traditional Chinese medicine.

FIGURE 2. The impact of Chinese herbal medicine (CHM) components on signal transduction pathways involved in immune activation. PMA, phorbol myristate acetate; MHC, major histocompatibility complex; TCR, T cell receptor; CRAC, calcium release-activated channel; Ca2+, calcium ions; B7, B cell activation antigen B7; CD28, Cluster of Differentiation 28; Src, proto-oncoprotein tyrosine-protein kinase Src; Syk, spleen tyrosine kinase; PK3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PLC-γ1, phospholipase C γ1; DAG, dimeric acidic glycoprotein (clusterin); IP3, inositol triphosphate; PDK1, pyruvate dehydrogenase lipoamide kinase 1; PKCB, Protein kinase C β; JNK, Jun N-terminal kinase; Akt, serine/threonine-specific protein kinase, also known as protein kinase B; β-TrCP, β-transducin repeat-containing protein; IKKα, IκB kinase α; IKKβ, IκB kinase β; IKKγ, IκB kinase γ; NFAT, nuclear factor of activated T cells; IκBα, IκB kinase α; NFκB, nuclear factor-κB; AP-1, activator protein 1.
Further investigation of network connections revealed that the CHM components PAB, saikosaponin d, and shikonin inhibit IKK-β and NFKB pathways simultaneously, while NFKB activation can be triggered by tamoxifen. As shown in Figure 2, the overall impact is to trigger immunotolerance (19–21). A number of other studies have also demonstrated network-based effects in inflammatory diseases and cancer with CHM compounds such as PHY906 (22), curcumin (23), and berberine (24).

In conclusion, the development of INBM will enhance our medical and health care system, and TCM has an important role to play in building the foundation for the approach. The route from TBBM to INBM has obstacles, from unraveling the crosstalk of multiple molecular pathways to understanding the CHM network effects, to digitalizing the large amounts of data. Nevertheless, TCM—and our ancestors’ wisdom—offers us a blueprint for establishing and implementing an INBM system for the betterment of humankind.

References

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The hunt for antibacterial and profrutictive botanicals

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1 the U.S. govern- ment estimtates that 45% of drugs in the United States can be attributed to fibrotic diseases, which are characterized by tissue scarring and often lead to chronic organ failure (1). Over the past several decades, researchers have investigated the un- derlying mechanisms involved in fibrosis and successfully pinpointed a number of promising targets, such as molecular mediators and effector cells. Moreover, a number of exceedingly potent and selective compounds against such targets have been devel- oped, although many have fallen short of expectations (2). For example, the only antifibrotic drug registered in Europe and in the United States, pirfenidone, has shown beneficial effects in patients with idiopathic fibrosis and fibrotic kidney disease; however, evidence for its efficacy lies in modest func- tional improvements, although its clinical efficacy on fibrosis remains elusive (3–5). On the other hand, a number of herbal medicinal products, such as those used in traditional Chinese medicine (TCM), have been reported as modulators of fibrosis, but definitive, comprehensive scientific evidence of botanicals as safe and effective antifibrotic therapies is lacking.

Botanicals: A double-edged sword

Botanicals are an important source of antifibrotic activities. For example, halofuginone, a derivative of febribugine isolated from the Tripterygium wilfordii Hook. F., is a potent antifibrotic agent that reduces one of the collagen cross-links. An additional two mechanisms are the inducible expression of collagen and the induction of matrix metalloproteinase-2 (MMP-2) and MMP-9 (6,7). In contrast, some botanicals are suspected of causing fibrosis. Herbs have been regularly reported as being associ- ated with chronic liver damage, from Africa to Asia and across the world (17–21). In clinical reports from Beijing and Shanghai, for example, herbs accounted for 21%–53.6% of drug-induced liver injury (18, 22, 23). In one of these studies, biopsy findings indicated that liver fibrosis is not uncommon in pa- tients with herb-associated liver injury (17, 24). Herbs have also been reported to be associated with fibrosis of the heart, mesentery, and kidney (24). For example, mesenteric fibrosis has been associated with long-term consumption of formulae containing Gardinia jasminoides Ellis fruits in Japanese patients and renal fibrosis is now well known to be induced by some Aristolochia taxa and other species containing aristolochic acids (AAA) (25–27). On repeated for medicinal use across a number of different regions, AA- containing plants are now recognized as a worldwide health threat and banned in most Western countries due to their association with urothelial cancers and with Balkan endemic nephropathy, which results from consuming grains contaminated by Aristolochia seeds (27). In vivo and in vitro studies indicate that many other herbs are associated with renal fibrosis. Notable exceptions include Dioscorea villosa

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FIGURE 1. Steps proposed for an efficacy-based drug development strategy, particularly well-suited for studying antibacterial botanicals.

Drug
Identify drug candidates to be tested in these models

Model
Develop and refine disease models suitable for drug discovery

Trial
Establish and maintain candidates on benefit-risk ratio

Mechanism
Perform mechanistic studies on efficacious drugs

Steps proposed for an efficacy-based drug development strategy, particularly well-suited for studying antibacterial botanicals.

Herbs and, 16 herbal formulas (14, 15). We found that Fuzheng Huayu and Salvia miltiorrhiza Bunge (SMB) root, a main component of Fuzheng Huayu, display the most potent in vitro antibacterial activities and all the formu- lae and herbs that were tested (14). Besides, in a recent system- atic review on clinical treatment of chronic hepatitis B—which took into account 138 trials, 62 proprietary traditional drugs and 16,393 patients—SMB and its extracts were pinpointed among the top five herbal entities reported to have the most potent antibacterial activities (16).

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J-Needle: Detecting the biological role of acupuncture

Authors: Christian Nattar*; Sandra Carrà*; Yuyuan Li*; Vincent Loy*; Vanyao Zhou*

Materials that appear in this section were not reviewed or assessed by Science Editorial Staff, but have been evaluated by an international editorial team consisting of experts in traditional medicine research.

Abstract

The mechanical interaction of a needle inserted into the skin by acupuncture elicits complex neurobiological responses that are still not well understood. To investigate the molecular mechanisms underlying acupuncture, we developed a new method called J-Needle, which uses a combination of functional proteomics and metabolomics to detect the biological role of acupuncture. J-Needle allows the identification of proteins and metabolites that are differentially expressed in response to acupuncture, providing insights into the mechanisms underlying acupuncture's therapeutic effects. The method is sensitive and robust, making it a valuable tool for future studies of acupuncture's biological effects. Further research is needed to validate the findings and explore the potential clinical applications of J-Needle.
throughput and low sensitivity of these ‘omics analyses. This can be imagined in the form of a nanobiosensor that is the size and shape of an acupuncture needle (hence, an “intelligent” needle or i-needle) (Figure 1C).

Towards this end, we recently created a principle of miniaturized platform, integrating revolutionary carbon nanotubes and nanographite petals, which can monitor five endogenous human metabolites using highly sensitive and selective nanosensors (20). The electronics needed to acquire and transfer the detected signal have already been sufficiently miniaturized (21) and can be powered by ultrathin polymer-based batteries (22) currently available on the market and able to meet the energy demands of the proposed i-needle (~80–130 μAh).

The challenge for the realization of the i-needle has already moved from the miniaturization to the integration step (23). Progress has already been made, based on recent reports of the measurement and transmission of temperature, pH, and endogenous metabolite data using single-platform enzyme-kinetic sensors (22, 24). The AT nanosensor is able to meet the energy demands of the proposed i-needle and can be powered by ultrathin polymer-based batteries (~80–130 μAh). The challenge for the realization of the i-needle has already moved from the miniaturization to the integration step (23). Progress has already been made, based on recent reports of the measurement and transmission of temperature, pH, and endogenous metabolite data using single-platform enzyme-kinetic sensors (22, 24). The AT nanosensor is able to meet the energy demands of the proposed i-needle and can be powered by ultrathin polymer-based batteries (~80–130 μAh).

Conclusions

Overall, it is our hope that this research can provide a more unified approach to understanding the complex nature of patient responses to acupuncture—including effects as diverse as the control of pain, degeneration, and inflammation—and to addressing fundamental issues in acupuncture treatment, such as the frequency of delivery, developing more precise therapeutic indications, and establishing proper “dosage” guidelines. These steps will undoubtedly encourage acceptance of acupuncture as a complementary and/or alternative personalized treatment, with important implications in a wide variety of areas including pain control, and degenerative and chronic inflammatory diseases, among others.

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Purinergic signaling in acupuncture

The proposed role of purinergic signaling in the physiological basis of acupuncture was first presented in 2009. Data showing that ATP is released from keratinocytes and other skin cells during acupuncture treatments lends weight to this hypothesis. ATP in turn activates P2X3 receptors on the sensory nerves in the skin, which then transmit those messages to motor neurons in the brain stem that control autonomic functions and modulate nociceptive activities. Here, we review and describe the recent evidence for purinergic signaling underlying acupuncture effects and propose ways to further test this hypothesis.

Introduction

It has been well established that adenosine 5’-triphosphate (ATP) is an intracellular energy source in cellular biochemistry. In 1970, Burstom et al. suggested that ATP acted as a nonadrenergic, noncholinergic neurotransmitter in the gut (1) and in 1972 he named the extracellular actions of ATP “purinergic” (since ATP is an A nucleotide), and formulated the purinergic signaling hypothesis (20).

In 2009, Burstom proposed that purinergic signaling might be involved in the physiological basis of acupuncture, mediating acupuncture effects. This hypothesis suggested that mechanical deformation of skin by needles or application of heat or electrical current leads to the release of large amounts of ATP from keratinocytes, fibroblasts, and other skin types (Figure 1). The released ATP then activates P2X3 ion channel receptors on sensory nerves within the skin and in afferent nerves that transmit messages via sensory ganglia and the spinal cord to the brain stem and hypothalamus. These brain regions contain motor neurons that control autonomic functions, including cardiovascular, gastrointestinal, respiratory, and urinogenital activities—common targets of acupuncture treatments. These sensory neuron messages also modulate the pathways that control autonomic functions in the cortex responsible for conscious awareness of pain and other central nervous system activities, including sleep regulation (21). A number of subsequent studies have been published that also implicate purinergic signaling in various aspects of acupuncture, detailed below.

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Supporting evidence for the hypothesis

Studies that have established the components involved in the purinergic signaling pathway include: (1) release of ATP (in response to mechanical or chemical stimulation)
from keratinocytes (4–6) and possibly from Merkel cells, which contain high levels of ATP (7, 8). ATP has also been shown to be released from keratinocytes upon heating (9), immunohistochemical data demonstrating the presence of P2X3 receptors on sensory nerve fibers in the skin (10–12) and tongue (13); (ii) In vivo tongue-ringed enamel preparation, mechanical activation of the tongue with De Frey hairs was shown to result in a discharge in the lingual sensory nerve fibers that was mimicked by ATP activation and blocked by P2X3 receptor antagonists (14); and (iv) both presynaptic inhibition via adenosine A1 receptors, and P2Y receptors, and enhancement via P2X and A2A receptors at synapses in the central nervous system have been reported (15).

Subsequent papers have built upon and extended evidence in support of purinergic signaling underlying acupuncture effects. Several studies have associated the skin cells affected by acupuncture techniques with purinergic signaling. For example, ATP has been shown to be released from human keratinocytes in response to mechanical stimulation by hypo-osmotic shock (16), as well as from keratinocytes in response to heat (17). Additionally, mast cells, which accumulate around the acupuncture needles, also release ATP in response to mechanical stimulation (18). Another skin cell type, human subcutaneous fibroblasts, can release ATP in response to bradykinin and histamine (19–20). Tsutsui et al. demonstrated that mechanical stimulation can evoke the propagation of calcium waves between human keratinocytes, induced by ATP and activation of P2Y2 receptors (21, 22), which is consistent with the earlier results from Koizumi et al. (5). Tuina (traditional therapeutic massage) and moxibustion (a traditional Chinese medicine therapy using a moxa, often made from dried mugwort, either used as a fluff or processed into a cigar-shaped stick) can be used indirectly, with acupuncture needles, or burned on to the patient’s skin may also act via the purinergic signaling pathway (23). Papers describing the release of ATP from human epidermal keratinocytes via connexin hemichannels and vesicles involving vesicular nucleotide transporter have recently been published (24–26). A 2010 study has claimed that adenosine, following breakdown of released ATP during acupuncture, can act as a presynaptic inhibitor of neurotransmission via A1 receptors, resulting in anti-nociceptive actions (27). Valuable reviews are available describing the neural pathways from different skin regions to structures in the brain stem and higher brain centers. These pathways are important because different acupuncture sites may activate different neural pathways impinging on specific nuclei in the brain stem that control autonomic functions potentially modulated by acupuncture (Figure 2) (28, 29).

Conclusions

Evidence in support of the hypothesis of purinergic signaling mediating the physiological mechanisms underlying acupuncture effects has been accumulating over recent years. To help further test this hypothesis, I propose that experienced acupuncturists focus on acupuncture sites that induce effects that can be quantified, such as an increase or decrease in heart rate or blood pressure, and identify specific neurons that are activated in the brain using noninvasive scanning techniques. If acupuncture-induced effects can be identified and quantified, researchers could then test whether ATP mimics the responses and if P2X3 receptor antagonists block the effects. Moreover, we suggest that researchers conduct experiments recording responses from sensory neurons in the skin and tongue in animal models and distinguish between low-threshold fibers involved in acupuncture and high-threshold fibers that mediate nociception, as well as recordings from the motor nerves in the brainstem responsible for autonomic functions.

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