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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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 an important, yet often underestimated, part of health care. TM is found in almost every country in the world and the demand for its services is increasing every day. TM can contribute to addressing a number of global health challenges of the 21st Century, in particular in the area of chronic, noncommunicable diseases and population aging.

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 acquire a better understanding of how to boost the global integration of TM into health systems, to benefit individuals seeking the right care, from the right practitioner, at the right time.

The two systems of traditional and Western medicine need not clash. Within the context of primary health care, they can blend together in beneficial harmony, taking advantage of the best features of each system and compensating for certain weaknesses in each as well. In an ideal world, TM would be an option, a choice, offered by a well-functioning, people-centred health system that balances curative services with preventive care. The challenge is to give TM its appropriate place in an integrated health system, to help all practitioners understand its unique and valuable contribution, and to educate consumers about what it can and cannot do. In other words, we need to modernize this rich resource and cultural heritage, and put it in its proper place in today’s world.

Margaret Chan, M.D.
Director-General, World Health Organization

A middle way for traditional medicine

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

In 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 preventing or 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 active 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.

Alan Leshner, Ph.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 (1254-1294), 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 credence in the early 1500s by the Herbalists Charter of Henry the VIII (1491-1547). His contemporary in China, Li Shihzen (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 good 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 acupunctu re 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 polysaccharides present in medicinal plants. Chemogenomics and network pharmacology have been applied to predict molecular targets and decipher the mechanisms of action of pure compounds or polypharmacotherapeutics found in TCM materia medica.

A better understanding of the philosophy of synergetic interactions of molecular targets and decipher the mechanisms of action of pure compounds or polypharmacotherapeutics present in TCM materia medica.

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The WHO Traditional Medicine Strategy 2014–2023: A perspective

The second strategic step under this objective recommends that T&M cannot be assured if there is not appropriate regulation of practices 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 uncertain regulatory and a lack of common or standard regulations for 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&M practices, products, and practitioners (2). This includes countries better regulating herbal medicines or T&M practices and to considering them.

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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&M 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&M can make to the health and well-being of individuals and communities (Box 1). In many countries, 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&M (15).

Governments and consumers are becoming more open to broadening T&M practices and to considering them as an integral part of health service delivery. In Africa, the number of national regulatory frameworks increased from one in 1999/2000 to 28 in 2013 (14). Across the Atlantic, the Ministry of Health in Brazil has developed a national policy on integrative and complementary practices (2), while in the eastern Mediterranean region, five member states report having regulations specifically for T&M practitioners (5).

The WHO Traditional Medicine Strategy 2014–2023

The second strategic step under this objective recommends that member states strengthen knowledge generation, intellectual and natural resources.

Objective 1: To strengthen quality assurance, safety, proper use, and effectiveness of T&M by regulating T&M products, practices, and practitioners.

TCM services cannot be assured if there is not appropriate regulation of practices and practitioners.
In China, there are about 440,700 health care institutions providing TM services, with 520,600 bed patients, including 1.6 million TM physicians and 3.0 million TM nurses. In hospitals, health care facilities, 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 medical institutions as conventional medical institutions. TM practitioners are allowed to practice in public and private clinics and hospitals. The public is free to choose their TM form of health care services, or follow the advice of their doctors.

Objective 3: To promote universal health coverage by integrating T&M services into health care service delivery and self-care health. One of the most significant questions raised about T&M is whether its potential benefits can be realized in the health care system, primarily primary health care. A first step is to capitalize on the potential of T&M to improve health services and health outcomes. Mindful of the traditions and customs of people around the world, the WHO member states should consider how T&M might support disease prevention or treatment as well as health maintenance and health promotion. This process should ensure 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&M into national health systems should be explored.

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

The WHO resolution WHA67.18 urges member states to adapt, adopt, and implement the WHO Traditional Medicine Strategy (WThMS) and WHO Traditional Medicine programs or work plans and to report to WHO on progress in implementing the resolution. The strategy also encourages WHO to support member states in implementing the strategy in the coming decade (11).

Conclusions

Around the world, T&M continues to grow in popularity. Progress in the regulatory gaining momentum, even as that of T&M practices and practitioners advances at a somewhat slower pace. Safety, quality, and effectiveness of T&M services is paramount, but cannot be ensured if appropriate regulation of practices 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&M to health, wellness, people-centred health care, and health systems, and various development challenges, while protecting patients from harm. By promoting the regulatory infrastructure necessary to prevent and mitigate the risks of T&M, the strategy is designed to bring about positive change in T&M policies. In both developed and developing economies, the practices of modern medicine exist side-by-side with traditional approaches and alternative remedies. For many living in developing economies, traditional healers and herbal remedies are the only source of available health care. In contrast, developed economies typically use these approaches as an optional complement to modern medicine, driven by patient preference. However, in both China and India, the ancient medical traditions—Tibetan Medicine and Ayurveda—are still in use and is entwined either in parallel or integrated with advanced modern care. In developing economies, the availability of certain health practices such as acupuncture, traditional Chinese medicine, massage, and meditation have grown in interest and are seen as gentler, “low-tech” complements to conventional care.

The persistence of such traditional practices in these settings suggests we have much to learn from them. Modern scientific methods can offer means to examine traditional practices. In this brief perspective, a few examples of traditional remedies are discussed to illustrate the issues we face in thinking about the intersection between modern medicine and traditional healers.

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A global scientific challenge: Learning the right lessons from ancient healing practices

Author: Josephine P. Briggs

The earth is a fundamental human value. Consequently, most cultures have sought after and used a broad variety of botanical medicines. This highlights the importance of considering different legislative frameworks in different countries, and ensures that information on quality and safety is shared so that products are used appropriately.

The second strategic direction is to recognize and develop T&M practice and practitioner regulations for education and training, skills development, services, and therapies. As more countries develop policies and regulatory frameworks, there is an opportunity to establish their effectiveness and identify ways in which they can be strengthened. T&M practitioner regulations can be addressed by benchmarking against appropriate reference standards.

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Acupuncture was compared to no acupuncture (in effect, a placebo) that relieves pain and reduces the need for 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 may 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 anecdotally, 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 benefit 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.

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

Thomas Hankemeier1,2, Mei Eduard P. van Wijk1,4, Jan van der Greef3,5

Western medicine and Chinese medicine developed within the context of different cultures and perspectives of the natural world. This model-dependent realism. Both models can be considered valid, each with its own context could generate a highly rewarding step forward for medicine.

The modern concept of the laws of nature emerged in the seventeenth century through the work of scholars such as Kepler and Galileo, with the most notable contributions coming from Newton and from Descartes, who emphasized a duality between the mind and the physical body. Philosophers have pondered whether more than one set of laws was possible. It seems that our conception of natural laws is characterized by a duality that encompasses the terrestrial aspect of humanity, and a circle, which represents the spiritual realm. The Taijī 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 medicine systemically. In the patient population on the left side of the figure a simplified, hierarchical view of molecules being organized into cells, with further consolidation into tissues, organs, and, ultimately, a whole organism. This illustrates the bottom-up approach practiced in Western biomedical science, where knowledge on the scientific understanding of signs and symptoms. The right side of the Vitruvian Man (Le proporzioni del corpo umano secondo Vitruvio) and the Taijī (Figure 1) illustrate the complex relationships among the various organs functions of the body. The background of the figure mirrors corresponds of the Greek philosopher, natural scientist, and mathematician, who is best known for his scientific understanding of the universe. A man is pictured within a square, which represents the terrestrial aspect of humanity, and a circle, which represents the spiritual realm. The Taijī symbolizes humanity as part of an eternal universe, has all the properties

Bridging the gap

Although there are many similarities between the Greek and Chinese medicine, the medical systems that arose in the West and in the East are quite distinct. Most notably, a highly reductionist, detailed view dominates in the West, whereas a more phenomenological, descriptive, and systems-based view holds sway in China. In recent decades, Western systems thinkers have started to combine theories 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 well as 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 biotechnical pathways and the dynamic organization of the body that characterize Western medicine. 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 relationship among the various organs functions of the body. The background of the figure mirrors corresponds of the Greek philosopher, natural scientist, and mathematician, who is best known for his scientific understanding of the complex relationships among the various organs functions of the body. 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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 (18, 19). Indeed, these coherent light functions may be directly involved in communication in addition to influencing biochemical networks (18, 19).

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 dynamics of such organization (Figure 2) 

Integration of Western and Chinese medicine thinking has enormous potential for synthesizing modern technological and traditional knowledge. Although Chinese and Western medicine are perceived as wholly distinct paradigms today, they are poised to merge in the arena of personalized systems medicine, where patients can take a greater role in managing their own health and wellness. Human–human relationships are critical for diagnosis and intervention in a biopsychosocial system. Therefore, both traditional Chinese and Western medicine can be much more than the sum of their parts. It is only a matter of time before there are attempts to integrate modern biophysical methodologies, such as the near infrared (NIR) and the thermal infrared (TIR) spectroscopies, into the holistic paradigm of traditional Chinese medicine, where the above-mentioned methodologies will be used to integrate the patient’s overall health status.

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. Zheng is fundamental for the diagnosis and treatment of diseases.

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 herbal recipes, such as Liu Wei Di Huang Wan and Jin Kui Shen Qi Wan, have long been used for the clinical 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 and a multiscale perspective, which makes them difficult to understand at a biological and mechanistic level, is the next step.

Zheng-guided disease research

Zheng has left us with little understanding of its underlying biology or the relationships between different Zhengs. Zhengs are the fundamental unit of diagnosis and treatment of diseases. Zhengs are deficiency-excess definitions to describe patients’ conditions, and this issue also applies to TCM. Moreover, Zhengs are dynamic with changing boundaries, overlapping symptoms, and these guidelines make it difficult to understand at a biological and mechanistic level. Zhengs are therefore critical for the diagnosis and treatment of diseases.

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Zheng-driven drug discovery

Despite considerable progress in genome, transcriptome, proteome, and metabolome through high-throughput screening methods and in rational drug design, drug discovery often encounters considerable costly failures that challenge the efficacy of the drug discovery system. 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 Zhengs, 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 (9). 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 Zhengs 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 q-bio study, where we identified the active compounds in the q-including and blood-toxifying 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 Zhengs. This process includes the initial collection and classification of herbal medicines; screening the ingredients for absorption, distribution, metabolism, excretion, and toxicity (ADMET); performing targeted drug screenings and tissue localization; constructing and analyzing networks; and finally identifying Zhengs/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 have the potential for enhancing energy metabolism and anti-inflammatory activity (12). The TCM to Zheng strategy can also help to elucidate the pharmacological effects of herbs and formulas.

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 fortune in the right technologies, to facilitate the understanding of multifactorial diseases and the development of new therapies.

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FIGURE 2. Zheng-driven drug discovery using Pi-deficiency syndrome and Si Jun Zi decoction as examples. (A) A “Zheng to TCM” procedure can build a pipeline from Pi-deficiency syndrome (PDS) to new effective herb/drug combinations by integrating omics data, network and pathway analysis, and pharmacokinetic evaluation techniques. SRS, Shi-Re syndrome, is a positive control for PDS. (B) An example of a “TCM to Zheng” strategy consisting of an entire evaluation process from Si Jun Zi decoction (SJZD) to PDS through a systems pharmacology strategy including text mining, ADMET (absorption, distribution, metabolism, excretion, and toxicity) screening, target identification, and network analysis to reveal the underlying mechanisms of SJZD activity and build new diagnostic methods for PDS.
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-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 suppression of a disease-associated molecular target. This narrow focus can miss a broader range of pathogens and 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 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

Figure 1. How integrated network-based medicine (INBM) works. TCM, traditional Chinese medicine.
The hunt for antibacterial and proﬁbrotic botanicals

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1. the U.S. government estimates that 45% of drugs approved in the United States can be attributed to ﬁbrotic diseases, which are characterized by tissue scarring and often lead to chronic organ failure (1).

Model

Drug Identify drug candidates to be tested in these models

Trial Establish and validate models based on beneﬁt-risk ratio for drug discovery

Mechanism Perform mechanistic studies with potential efficacious drugs

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development of CHMs can be combined with digitalized medicine advances such as systems biology techniques, computational technologies, and translational research to provide the foundation for a “personalized” INBM strategy. Our proposal for a new personalized approach to cancer treatment provides just one example of the use of CHM for a network-based treatment. We have recently investigated two CHMs, Panax ginseng and Rhizoma Coptidis, and found that they inhibit cancer growth, prompting us to investigate the effects of these herbs on cancer cell metabolism. Using profiling methods such as liquid chromatography, mass spectrometry, and nuclear magnetic resonance, we found alterations to the glucose and fatty acid metabolic pathways at a network level (10, 11). We therefore speculate that metabolic biomarkers could be used to identify subgroups of patients with lipid- and glucose-related metabolic disorders. These patients are likely to benefit most from the herbs’ active compounds. The approach could be further refined by the application of ‘omics technologies to optimize the synergistic effect of the herbal remedies (12–15). With clinicians and basic researchers working together to create a database of personal therapeutic responses, continual feedback to herbal formulations would become possible.

From TBDM to INBM How do we turn the INBM system from an idea into a practice? One major step forward would be the systematic quantiﬁcation and validation of individual CHM components. Such a database would help deﬁne parameters for the combination treatments. One requirement is to identify, monitor, and control the major metabolic pathways, as altering a key molecular switch could have unintended, ampliﬁed effects on the network. A number of studies have begun to identify the speciﬁc network effects of various CHM-extracts or CHM-derived chemicals, including red yeast rice, Tripterygium wilfordii Hook F., Ganoderma lucidum, San Miao Wan, arsenic sulﬁde, astragaloside IV, Artemisia capsillaris Thumb, Radix Angelica Sinensis, Reallagradinucu, longa L., and NFAT (nuclear factor of activated T cells) pathway, resulting in immunotolerance (19–21). In another example, we have recently found that an extract of Schisandra chinensis is safe and effective antifibrotic therapeutics is lacking. In contrast, some botanicals are suspected of causing liver injury. Fibers have been regularly reported as being associated 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 same studies, biopsy ﬁndings indicated that liver ﬁbrosis is not uncommon in patients with herb-associated liver injury (18). Herbs have also been reported to be associated with liver injury, the heart, mesentery, and kidney (24). For example, mesenteric ﬁbrosis has been associated with long-term consumption of formulations 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 (AAAs) (25–27). On the other hand, a number of different regions, AAAs-containing plants are now recognized as a worldwide health threat and banned in most Western countries due to their association with carcinoma of the bladder associated with Balkan endemic nephropathy, which results from consuming grains contaminated by Aristolochia seeds (27). In vitro and in vivo studies indicate that many other herbs are associated with renal ﬁbrosis. Notable examples include Discocorea villosa
L. rhizome, an herb commonly used in Australia to treat symptoms of menopause and rheumatoid arthritis (40). Debx. have potent in vitro profibrotic activities (41), and Debx. has been recently linked to end-stage renal disease (ESRD) in Taiwan (15). The impact of identifying and avoiding exposure to pro- fibrotic botanicals is profound. For instance, one of the cases reported here involved a case report by the U.K. Medicines and Healthcare Products Regulatory Agency (30) illustrating that medicinal plants can cause harm. Among the 181 cases submitted to the U.K. Medicines and Healthcare Products Regulatory Agency (30) between 1997 and 2003 (31), many clinical reports on herbal remedies have turned Taiwan into one of the few regions with retarded domestic clinical trials to prove antifibrotic effects and invites interregional collaboration (11). The banning of AA-con- tents herbs, together with other efforts such as public-aware- ness campaigns, education of patients, funding for research into chronic kidney disease, and provision of integrated care, has turned Taiwan into one of the few regions with retarded re- solution of evidence base (23).

Moving forward

It is worth emphasizing that innovation is needed to develop high-quality in silico, in vitro, and in vivo strategies that can facilitate the investigation of antifibrotics and detect profibrotic activities. Such a strategy is highly dependent on disease modeling. Because evidence-based medicine is a relatively new concept in many countries (34), many clinical reports on herbal treatment of fibrotic diseases are criticized for poor quality. Disease modeling for the conditions here reviewed include liver fibrosis (35, 36), pulmonary fibrosis (36), multiple sclerosis (36), and adhesive small bowel obstruction (37). An efficacy-based strategy ultimately demands high-quality clinical trials to prove antifibrotic effects and invites interreg- ular cooperation to improve the monospecificity of profibrotic botanicals, which is challenging due to the insidious nature of fibrosis and the variability in the distribution channels and legal status of botanicals (38, 39).

Finally, traditional use is only indicated but certainly not a proof of either safety or efficacy (40). To harness and under- stand botanically mediated mechanotransductive therapeutic pathways, and for the prevention of fibrotic diseases, future research and innovation must focus on efficacy and safety, and must be built on and co-ordinated with policies, which we have recently defined at length (41). Development and refinement of good practices, however, can only be achieved with sustainable funding.

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14. J. Liu, in Acupuncture Across Regions: Shiny definitions of acupuncture (acupoints, meridians, and energy flow or qi) with anatomical structures and biochemical pathways. Additionally, a unified scientific theory to explain the diverse effects of acupuncture (from pain control to immu- notherapy) is lacking, despite important advances in the association of purinergic signaling with the effects of acu- puncture on pain control. As new technologies simultaneously offer enhanced capacities to explore breadth (using ’omics) and depth (using -omics) of biochemical events, we propose the innovative conjugation of these approaches into an in silico, in vitro, and in vivo strategy as a means to overcome the abovementioned limitations.

Acupuncture is being widely debated in the medical community as a potential alternative or complementary treatment for many diseases (1). There are numerous challenges to achieving a consensus over the use of acupuncture in a medi- cal environment, including: filling the gap in knowledge about the underlying molecular mechanisms of acupuncture, and (ii) interpreting traditional categories (such as acupoints, med- rids, and qi) and therapeutic indications within an evidence- based medicine framework. Important questions aimed at increasing our understanding of the molecular mechanisms of acupuncture stimulation have been posed, mostly regarding pain control (2), functional recovery of tissue (2), and immunomodulation (4) (42). A breakthrough in experimental (in silico, in vitro, in vivo) and clinical studies is thus requisite for better understanding of acupuncture.”

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**J-Needle: Detecting the biological mechanisms of acupuncture**

**Authors:** Christine Nardini1,2*†, Sandra Carrà1*, Yvannah Liu1, Valentine Yu1,2‡, Xiaoyan Zhou†

**A**

The long standing obstacle to the full integration and acceptance of acupuncture in conventional medicine lies in the difficulty of relating the uniqueness of acupuncture (acupoints, meridians, and energy flow or qi) with anatomical structures and biochemical pathways. Additionally, a unified scientific theory to explain the diverse effects of acupuncture (from pain control to immuno-therapy) is lacking, despite important advances in the association of purinergic signaling with the effects of acupuncture on pain control. As new technologies simultaneously offer enhanced capacities to explore breadth (using ’omics) and depth (using -omics) of biochemical events, we propose the innovative conjugation of these approaches into an in silico, in vitro, and in vivo strategy as a means to overcome the abovementioned limitations.

Acupuncture is being widely debated in the medical community as a potential alternative or complementary treatment for many diseases. There are numerous challenges to achieving a consensus over the use of acupuncture in a medical environment, including: filling the gap in knowledge about the underlying molecular mechanisms of acupuncture, and interpreting traditional categories (such as acupoints, meridians, and qi) and therapeutic indications within an evidence-based medicine framework. Important questions aimed at increasing our understanding of the molecular mechanisms of acupuncture stimulation have been posed, mostly regarding pain control, functional recovery of tissue, and immunomodulation. A breakthrough in experimental (in silico, in vitro, in vivo) and clinical studies is thus requisite for better understanding of acupuncture’s effects. The homeostatic effects of type 2 EMT include local changes in purinergic signaling, inflammation control, and cell-matrix remodelling at the cellular level. By contrast, acupuncture is recommended for systemic diseases like rheumatoid arthritis and is thought to act in a more global fashion.

Using the framework we propose here, we can investigate the long range, systemic effects of mechanotransduction by building on what has already been reported about acupuncture and the interaction of the biochemical events with the system. To explore the long range effects of acupuncture, multomic analysis of molecular events—occurring proximally (acupoint), distally from the acupuncture point (limb or organ), and systemically (blood and gastrointestinal microbiome)—can be used to construct a spatial analysis (17). This information can then be used to create a systems biology and systems medicine expression, in addition to later time points (Figure 2A) to construct a systems biology view (network) of the biochemical events. To build such networks and identify new targets for diagnoso- sis and therapy, we can directly apply the method described for the different ‘omics approaches (Figure 1B), coupled with the requisite temporal and spatial resolution of the data (19). This type of systems approach can identify the most important mol- ecules from the thousands to tens-of-thousands of interactions and hundreds-to-thousands of molecules analyzed, also taking into account the fact that one molecule might play a role in causing or modulating the pathways.

Furthermore, the identification of additional markers is made possible with a complementary approach to the high-
Progress has already been made, based on recent reports of miniaturized devices that are able to meet the energy demands of the proposed insertional acupuncture machine (~80–130 μAh). An energy-autonomous device that is able to transmit information remotely and in real-time.

Network analysis and simulations allow identification of molecules that can be monitored as markers of the progress of the therapy. A unified approach to understanding the complex nature of acupuncture involves the integration of revolutionary carbon nanotube microelectronics and nanobiotechnology. The miniaturized platform, integrating revolutionary carbon nanotubes and nanographite petals, which can monitor five endogenous human metabolites using highly sensitive and selective biosensors.

However, it is our hope that this research can provide a more precise therapeutic indication, and establishing treatment, such as the frequency of delivery, developing and to addressing fundamental issues in acupuncture as the control of pain, degeneration, and inflammation—those sensory nerve endings can be imagined in the form of a nanobiochip that is the size of a needle's eye (Figure 1C).

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-based needle technology (24). A number of subsequent studies have been published that also implicate purinergic signaling in various acupuncture endpoints.

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).

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2 receptors at synapses in (Reproduced from 28, with indicated with gray shadow.

Acupuncture stimulation are of the body. Brain areas treatment from various parts following acupuncture (sensory) neural impulses concentration of the central neural

Schematic illus-

1 and P2Y receptors, and blocked by P2X3 receptor antagonists (16).

as brain derived neurotrophic factor (BDNF) expression via inhibitors of neurotransmission via A1 receptors, resulting in neurotransmitter via A, 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).

Purinergic signaling and electroacupuncture

Electroacupuncture is a form of acupuncture where a small electric current is passed between pairs of acupuncture needles. This is thought to augment traditional acupuncture and is believed to be particularly helpful in treating pain. The supraspinal antinociception effect of electroacupuncture has been associated with P2X3 receptor activation in the midbrain periaqueductal gray region (30). Moreover, the analgesic effect of electroacupuncture on chronic neuropathic pain has been shown to be mediated by P2X3 receptors in rat dorsal root ganglion neurons (31). Following these studies, electroacupuncture was shown to result in a reduced expression of P2X3 and P2X2 receptors in the dorsal root ganglion of rats with chronic neuropathic pain (32) and visceral hypersensitivity (33). Electroacupuncture at He-Hu points can also reduce P2X4 receptor expression in colon and spinal cord in visceral hypersensitivity (34). Moreover, in a review by Lin et al., the neuroprotective effects of acupuncture were reported to act via increasing brain derived neurotrophic factor (BDNF) expression via stimulation of ATP (35).

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 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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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), and immunohistochemical study demonstrating the presence of P2X3 receptors on sensory nerve fibers in the skin (10-12) and tongue (13); (ii) in rat dorsal root ganglion, spinal nerve roots 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 A, and P2Y receptors, and enhancement via P2X2 and A 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

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), and immunohistochemical study demonstrating the presence of P2X3 receptors on sensory nerve fibers in the skin (10-12) and tongue (13); (ii) in rat dorsal root ganglion, spinal nerve roots 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 A, and P2Y receptors, and enhancement via P2X2 and A receptors at synapses in the
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