

FEATURE ARTICLE

Integrative Oncology Meets Immunotherapy: New Prospects for Combination Therapy Grounded in Eastern Medical Knowledge

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enhancers of the body's immunity.

ABSTRACT As cancer rates rise globally, standard care is being questioned; new approaches involving immune therapies are emerging. With this shift comes a corresponding shift in the use and potential of herbal medicines and extracts. The focus of this article, which has evolved from a presentation at the Second Beijing International Symposium on Integrative Medicine (BISIM May 19-20, 2012), is particularly on Chinese medicine, but is generalizable to Eastern medicine more broadly and to other herbal traditions. Until recently, herbal and related treatments have been used as adjuvants to conventional care – for reducing side-effects, enhancing cytotoxicity, and sometimes, undesirably counteracting the efficacy of chemotherapy and radiation. Now, in the context of a new class of immune-based cancer therapies, herbal and other complementary modalities are looked at as

WHO data reveal that 70% of cancer deaths occur in low- and middle-income countries and that 30% of all cancers could have been prevented.⁽¹⁾ Recent research in the UK has found that about 43% of new cancers are caused by avoidable life choices including smoking, drinking and poor diet, and that these factors account for 50% of all cancer deaths.⁽²⁾

In the US alone, the National Institutes of Health estimates overall costs of cancer in 2010 at \$263.8 billion: \$102.8 billion for direct medical costs (total of all health expenditures); \$20.9 billion for indirect morbidity costs (cost of lost productivity due to illness); and \$140.1 billion for indirect mortality costs (cost of lost productivity due to premature death).⁽³⁾ In China, cancer is now the leading cause of urban deaths. Data from the Chinese Ministry of Health implicate cancer in almost a quarter of all deaths.⁽⁴⁾ Accordingly, cancer control has become one of the most important national issues that the Chinese government is dealing with.⁽⁵⁾

As cancer incidence grows worldwide, people with cancer increasingly seek a broad range of approaches for increasing their chances of survival and enhancing their quality of life. Reflecting this trend, the new field of integrative oncology has spawned fresh directions in cancer prevention, care and outcomes. Indeed, research assessing the prevalence

of complementary and alternative medicine (CAM) in a US comprehensive cancer center found that 83.3% of patients had used at least one CAM approach and 62.6% had used vitamins and herbs.⁽⁶⁾

INTEGRATIVE ONCOLOGY

Integrative oncology has been defined as: "a science and a philosophy that focuses on the complexity of the health of cancer patients and proposes a multitude of approaches to accompany the conventional therapies of surgery, chemotherapy, molecular therapeutics, and radiotherapy to facilitate health."⁽⁷⁾

Problems with Conventional Cancer Therapy

The American Cancer Society's Guide for Understanding Chemotherapy states: "Cancer cells tend to grow fast, and chemo drugs kill fast-growing cells. But because these drugs travel throughout the body, they can affect normal, healthy cells that are fast growing, too. Damage to healthy tissue causes side-

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effects... The normal cells most likely to be damaged by chemo are blood-forming cells in the bone marrow; hair follicles; and cells in the mouth, digestive tract, and reproductive system. Some chemo drugs can damage cells in the heart, kidneys, bladder, lungs, and nervous system."⁽⁸⁾

As use by patients and physicians of herbal adjuvant therapy for cancer has grown, a body of research has begun to emerge – to reduce side-effects and to increase efficacy of standard treatment. Preclinical and clinical studies have demonstrated that Chinese herbal medicines are capable of suppressing tumor progression, increasing the sensitivity of chemo- and radiotherapeutics, improving an organism's immune system function, and lessening the damage caused by chemo- and radiotherapeutics. The trend towards standardised Chinese herbal preparations for cancer therapy is worthy of note. Here, classical ingredients and clinical insights from Chinese medicine combine to produce herbal extracts according to modern scientific standards.

(a) **PHY906**. In work led by Prof. Cheng Yung-Chi of Yale University, Phase I and Phase II clinical studies have shown a combination of four traditional Chinese herbs to decrease gastrointestinal toxicity from the chemotherapeutic drug CPT-11 (Irinotecan).⁽⁹⁾

Known as PHY906, the combination is a spray dried aqueous extract of: *Glycyrrhiza uralensis* Fisch; *Paeonia lactiflora*. Pall; *Scutellaria baicalensis*, *Ziziphus jujuba* Mill. These herbs are reported to have been used in combination in Chinese medicine for more than 1800 years, particularly for gastrointestinal distress, including diarrhea, cramps, nausea and vomiting. In their contemporary combination as PHY906, the product is a standardised formulation of the four herbs, produced via a proprietary technology known as Phytomics QC. In laboratory research, it was found that PHY906 enhances the antitumor activity but decreases global toxicity of Irinotecan.⁽¹⁰⁾

(b) **TJ-41**. This formulation consists of a crude standardized extract from ten herbs: *Astragalus membranaceus* 10.0 g, *Panax ginseng* 10.0 g, *Atractylodes lancea rhizome* 10.0 g, *Angelicae sinensis* 7.5 g, *Radix bupleuri* root 5.0 g, *Glycyrrhiza glabra* root 3.8 g, *Rhizome cimicifuga* 2.5 g, *Ziziphus ziziphus* 5.0 g, *Citrus unshiu* peel 5.0 g, and *Zingiber*

officinale 1.3 g. Pre-clinical and clinical studies have demonstrated that TJ-41 formula may inhibit tumor cell proliferation, enhance immune activity of lymphocytes, and improve cancer patients' wellbeing. Research has found that TJ-41 inhibited the proliferation of human breast cancer cell lines dose dependently, and that combined treatment of TJ-41 and 5-FU significantly potentiates the apoptotic effects of 5-FU in both breast cancer cell lines used. The researchers noted that, taken together, the data suggest that TJ-41 might provide a novel chemotherapeutic treatment for breast cancer.⁽¹¹⁾

(c) **Triptolide**. This diterpene triepoxide from the Chinese plant *Tripterygium wilfordii* (Lei gong teng or Thunder God Vine), has shown antitumor activities in a broad range of solid tumors, as well as inducing apoptosis in various leukemic cell lines and primary acute myeloid leukemia (AML) blasts.⁽¹²⁾ *In vitro* and *in vivo* research found Triptolide: (1) significantly reduced pancreatic cancer cell viability *in vitro*, (2) had no effect on the viability of normal pancreatic ductal cells, (3) decreased pancreatic cancer growth *in vivo*, (4) significantly decreased local-regional tumor spread, and (5) the control group of mice had extensive local invasion into adjacent organs, including the spleen, liver, kidney, and small intestine.⁽¹³⁾

In a 2012 study examining anti-leukemic activity of MRx102, a Triptolide derivative currently in preclinical development, MRx102: (1) showed potent anti-leukemic activity both *in vitro* and *in vivo*, (2) had the potential to eliminate AML stem/progenitor cells and (3) overcome micro-environmental protection of leukemic cells and (4) was found to warrant clinical investigation.⁽¹⁴⁾

LIMITATIONS OF CHEMOTHERAPY

Despite the promise of herbal approaches in mitigating the side-effects of chemotherapy and, in some instances, increasing the effectiveness of chemotherapy, there is still growing reluctance among people with cancer to submit to the debilitating and often uncertain prospects of chemotherapy. An Australian investigation into the contribution of chemotherapy to 5-year survival in 22 major adult malignancies, showed that the overall contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults was estimated to be 2.3% in Australia and 2.1% in the USA. The authors

concluded: "As the 5-year relative survival rate for cancer in Australia is now over 60%, it is clear that cytotoxic chemotherapy only makes a minor contribution to cancer survival."⁽¹⁵⁾

In Rome, a meta-analysis of studies was conducted, with a total subject population exceeding 7,000. The researchers found that studies designed to determine if cisplatin- or carboplatin-based chemotherapy improves survival over surgery, showed chemotherapy to have a relative benefit of only 7%–12% and an absolute benefit ranging from 2.5% to 4.1%. The authors noted that, while this was statistically significant, the small magnitude of benefit seen with this large population does raise important issues when weighing risks and benefits of treatment for individual patients.⁽¹⁶⁾

In a US study, patients assigned to early palliative care had a better quality of life than did patients assigned to standard care. The study also found that fewer patients in palliative care than in the standard care had depressive symptoms. Significantly, patients receiving early palliative care had less aggressive care at the end of life but longer survival.⁽¹⁷⁾

In view of the severe side-effects of chemotherapy and persistent questions about its benefits, a move towards immune-based therapies is gaining ground as both an adjuvant and potentially a first line treatment for cancer. There are significant synergies between the goals and effects of cancer immunotherapy and of integrative Chinese medicine.

IMMUNE BASED APPROACHES

Cancer Immunotherapy

The American Cancer Society describes immunotherapy as a "treatment that uses your body's own immune system to help fight cancer." This is done by stimulating the immune system to attack malignant tumor cells responsible for the disease—either through immunization of the patient (e.g., by administering a cancer vaccine), or through the administration of therapeutic antibodies as drugs.⁽¹⁸⁾

With vaccines, the patient's immune system is recruited to destroy tumor cells by the therapeutic antibodies. In the case of administration of antibodies as drugs, the patient's own immune system is trained to recognize tumor cells as targets to be destroyed.

Another major entity of cancer immunotherapy is cell-based immunotherapy. Here, immune cells such as the natural killer cells (NK cells), lymphokine activated killer cell (LAK), cytotoxic T lymphocytes (CTLs), dendritic cells (DCs), etc., may either be activated *in vivo* by administering certain cytokines, such as interleukins, or they can be isolated, enriched and transfused to the patient to fight against cancer.

In the US, a Cancer Immunotherapy Consortium (CIC) was established in 2002 to improve patient care by making cancer immunotherapies part of the standard-of-care in oncology.⁽¹⁹⁾

Cell-based Immunotherapy

Introduced by Rosenberg, et al⁽²⁰⁾ at the NIH, and now standard practice in Japan, this involves: (a) isolating either allogenic or autologous immune cells, (b) enriching them outside the body, and (c) transfusing them back to the patient.

The injected immune cells are highly cytotoxic to the cancer cells.

Among these approaches, DC therapy has come to be seen as highly promising. In 2011, Dr. Ralph M. Steinman posthumously shared the Nobel Prize in Physiology for Medicine for his discovery of the DC and its role in adaptive immunity. In Steinman's work signals arising from the innate immune response and sensed by DCs were shown to control T cell activation.

The Stanford University Cancer Institute reports that: "The first attempt to use DCs as cancer vaccines in humans was made by Edgar Engleman and Ronald Levy at Stanford, who isolated DCs from patients with non-Hodgkin's lymphoma who had failed conventional chemotherapy, loaded the cells with immunoglobulin idotype obtained from the patient's tumor, and re-injected the antigen-loaded cells back into the patients. Remarkably, most of the treated patients developed T cell mediated immune responses to their tumor-specific antigen and of the first six patients, two had complete remissions."⁽²¹⁾

Subsequent studies have shown that antigen-loaded DC vaccinations represent a safe and promising form of immunotherapy for a wide range of malignancies. In examining why there are differences

in success rates among different patients using DC, further research has suggested that access of DCs to tumor antigens, as well as the ability of these cells to mature, are critical for the induction of an efficient immune response. Efficacy is also linked to the number of tumor DCs present and the tumor environment. The site for injection of DCs is also under examination to determine the optimal method for ensuring efficacy. Methods include systemic injection; injection of DC's into lymph nodes; intra-tumoral injection.

Current clinical research in integrative immunotherapy is examining the effects of combining with such natural products as curcumin, derived from the potent anti-inflammatory root of turmeric, and Biobran, a Japanese product.⁽²²⁾

Curcumin, (diferuloylmethane), a dietary pigment from the root of turmeric (*Curcuma longa*), is a safe, affordable, and efficacious agent to use in cancer therapy. A powerful anti-inflammatory agent,^(23,24) curcumin has been found to selectively kill cancer cells and not normal cells.^(25,26) Importantly for a consideration of curcumin's role in integrative cancer immunotherapy are its potent immunomodulatory effects.^(27,28)

Ravindran and colleagues at the Anderson Cancer Center in Texas, report that curcumin modulates the growth of tumor cells through regulation of multiple cell signaling pathways. These include cell proliferation pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-xL, cFLIP, XIAP, c-IAP1), caspase activation pathway (caspase-8, 3, 9), tumor suppressor pathway (p53, p21) death receptor pathway (DR4, DR5), mitochondrial pathways, and protein kinase pathway (JNK, Akt, and AMPK).⁽²⁹⁾ The authors also note that because curcumin mediates its effect through multiple cell signalling pathways, the likelihood of developing resistance to it is less. Because of curcumin's ability to kill tumor cells and not normal cells, the authors argue that curcumin is an attractive candidate for drug development.

As noted, in addition to curcumin, the Japanese product BioBran MGN-3 (or just Biobran) is also being used in integrative cancer immunotherapy.

Biobran is a natural blend of hemicelluloses

(*arabinoxylan* compound or b-1, 4 *xylophyronase hemicellulose*) produced from rice bran broken down (partially hydrolyzed) using Shitake mushroom enzymes (*lentius edodes mycelia* extract). It has been shown to have a strong modulating effect on the immune system, helping maintain both optimum immunity and working to reduce the risk of immune-related diseases. Of importance to integrative cancer immunotherapy, Biobran has been shown to activate human monocyte-derived DCs.^(30,31) A three-year randomized controlled clinical study has found that Biobran enhances the effects of interventional therapies for the treatment of hepatocellular carcinoma.⁽³²⁾

MONOCLONAL ANTIBODY THERAPY

A monoclonal antibody can: (a) be directed to attach to certain parts of a cancer cell, thus marking the cancer cell and making it easier for the immune system to find; (b) block growth signals of cancer cells; (c) stop new blood vessels from forming, thus depriving cancer cells of the oxygen and nutrients needed to keep them growing; and (d) deliver radiation to cancer cells by combining a radioactive particle with a monoclonal antibody. This allows targeted radiation to be delivered to cancer cells and not to surrounding cells.

The US Food and Drug Administration has approved a number of therapeutic monoclonal antibodies for use with cancer patients.

In a case study of a single patient with metastatic melanoma, who had not responded to standard treatment, Dr. Cassian Yee's group at the Fred Hutchinson Cancer Research Center in Seattle, showed that the infusion of a clonal population of CD4+ T cells with specificity for a single tumor-associated antigen caused complete regression of a tumor.⁽³³⁾ The authors note that during regression of the tumor, the clone appears to have induced the patient's own T cells to respond to other antigens of the tumor. Through the successful reversal of advanced skin cancer within eight weeks, this study has become widely viewed as a landmark in the treatment of cancer in general.

The emergence of immunotherapy provides opportunities for herbal medicines to contribute beyond reducing side-effects of toxic chemicals. Now they have a role in enhancing the body's natural immunity in support of the vaccines and targeted

immune responses of cancer immunotherapy.

Recent research has demonstrated that: (a) the presence of CD8+ T cells within a tumor is associated with a good prognosis; (b) eradication of all malignantly transformed cells within a tumor requires that the intra-tumoral concentration of cytolytically active CD8+ effector T cells remain above a critical concentration until every tumor cell has been killed.⁽³³⁾

These findings have stimulated two initiatives in the field of cancer immunotherapy that focus on the tumor microenvironment: (1) The development of an immune score as part of the routine diagnostic and prognostic evaluation of human cancers, and (2) the development of combinatorial immune-based therapies that reduce tumor-associated immune suppression to unleash pre-existing or therapeutically-induced tumor immunity.⁽³⁴⁾

In view of this, the Society for Immunotherapy of Cancer (SITC) is focusing its research efforts on the development of integrative cancer immunotherapies that sculpt the tumor microenvironment to promote definitive tumor rejection.⁽³⁵⁾ This would seem to open the door for parallel research on natural products and their potential to 'sculpt the tumor microenvironment to promote definitive tumor rejection'.

NATURAL PRODUCTS AND IMMUNOTHERAPY— CHINESE MEDICINE

Already research is showing anti-cancer effects of Chinese medicines and other herbal products and the potential for these to synergise with new advances in immunotherapy.

Ling Zhi (*Ganoderma lucidum*) described in *Shennong's Classic of Materia Medica* (Shen Nong Ben Cao Jing) in the 1st–2nd century CE, has long been used in Chinese medicine for longevity and health. Ling Zhi has been shown in two randomized and one nonrandomized trials to enhance cellular immune responses and mitogenic reactivity of cancer patients.⁽³⁶⁾

Goji Berry (*Lycium barbarum*; *L. chinense*) is the common name for the fruit of two closely related species: *Lycium barbarum* (Níngxià gǒuqǐ) and *L. chinense* (gǒuqǐ). Goji berries, used in Chinese medicine to tonify Kidney (Shen) and Liver (Gan) yin

and Lung (Fei) Yin, contain 18 amino acids, 21 trace elements, as well as vitamin A (beta carotene), B1, B2, B6 and vitamin E. Of relevance to this paper, Goji berries are rich in *Lycium barbarum* polysaccharides (LBP), which exhibit anticancer, antioxidant, hypoglycemic, and immunological activities.⁽³⁷⁻³⁹⁾ *In vitro* research on LBP-induced interruption of the cell cycle in human colon carcinoma cells showed that LBP treatment inhibited both cancer cell lines in a dose-dependent manner, suggesting that LBP is a candidate anticancer agent.⁽⁴⁰⁾

A randomized controlled trial on the effects of a milk-based formulation of *Lycium barbarum* on immune functions in the elderly, especially vaccine response, found that those receiving the formulation had significantly higher post-vaccination serum influenza-specific immunoglobulin G levels and seroconversion rate versus placebo.⁽⁴¹⁾

In a clinical study on LBP, 79 advanced cancer patients were treated with LAK/IL-2 combined with LBP.⁽⁴²⁾ The response rate of patients treated with LAK/interleukin-2 (IL-2) plus LBP was 40.9% while that of patients treated with LAK/IL-2 was 16.1% ($P < 0.05$). The mean remission in patients treated with LAK/IL-2 plus LBP also lasted significantly longer. LAK/IL-2 plus LBP treatment led to a more marked increase in NK and LAK cell activity than LAK/IL-2 without LBP. The authors conclude that their results indicate that LBP can be used as an adjuvant in cancer therapy.

Cordyceps. With use recorded in Chinese records in 620 AD, it was reportedly used to enhance health, fertility and enhanced vitality. In research on a *Cordyceps militaris* extract (CME) conducted at Daejeon University in Korea and using human umbilical vein endothelial cells (HUVEC), CME was found to have cytotoxic potency *in vitro*.⁽⁴³⁾

Angiogenesis, the process of new blood vessel formation from existing blood vessels is a natural response to restriction in blood supply to tissues, known as ischemia. The Daejeon study found that CME generates anti-angiogenic and anti-tumor effects by reducing matrix metalloproteinases 2 (MMP-2), the enzyme encoded by the MMP-2 gene, which is strongly correlated with tumor invasion and metastasis. CME also produced an anti-angiogenic effect by reducing expression of the angiogenic factor

basic fibroblast growth factor (bFGF).

Stem Cell Research

The Stem Cell Information website of the US National Institutes of Health states: "Studying stem cells will help us understand how they transform into the dazzling array of specialized cells that make us what we are. Some of the most serious medical conditions, such as cancer and birth defects, are due to problems that occur somewhere in this process. A better understanding of normal cell development will allow us to understand and perhaps correct the errors that cause these medical conditions."⁽⁴⁴⁾

Stem cell research and treatment is currently being practiced at a clinical level in China.⁽⁴⁵⁾ Stem cells are thought to mediate repair via five primary mechanisms: (1) providing an anti-inflammatory effect, (2) homing to damaged tissues and recruiting, endothelial progenitor cells, that are necessary for tissue growth, (3) supporting tissue remodelling over scar formation, (4) inhibiting apoptosis, and (5) differentiating into specific organ tissue.

In cancer treatment, researchers consider that the key to finding a cure for cancer is to inhibit proliferation of cancer stem cells. Recent preclinical trials have shown that low doses of the anti-diabetic drug metformin, believed to be the most widely prescribed anti-diabetic drug in the world, may effectively destroy cancer stem cells, a group of cells that are considered to be responsible for tumor initiation and, because they are resistant to standard chemotherapies, tumor relapse.⁽⁴⁶⁾

In regenerative therapy, stem cells are generally isolated either from the patient's bone marrow or from adipose tissue. Bone marrow contains mesenchymal stem cells (MSCs), multipotent stem cells that can differentiate into osteoblasts, chondrocytes, myocytes, adipocytes and beta-pancreatic islets cells. MSCs can also trans-differentiate into neuronal cells. Recent research has shown that a stem cell product derived from the freshwater plant *Aphanizomenon flos-aquae* induced mobilization of stem cells from the bone marrow to migrate to sites of tissue damage and participate in tissue regeneration.⁽⁴⁷⁾ News reports in June 2012 indicate that cordyceps is now about to be added to this extract, along with a proprietary formulation of fucoidan, a sulfated polysaccharide

found mainly in various species of brown algae and brown seaweed.

There are many other products that merit mention. Indeed, work in India on the immunomodulatory effects of Ayurvedic plants in the context of cancer therapy is also building momentum – some of these plants are common to both Ayurveda and Chinese medicine.⁽⁴⁸⁾ What this growing body of evidence serves to highlight is the immunomodulatory effects of these plants and extracts and their potential suitability as partners in integrative cancer immunotherapy. Research in integrative cancer immunotherapy might consider, whether there are natural products that: (1) enhance the efficacy of conventional stem cell therapy with cancer; (2) stimulate natural stem cell expression without the need for harvesting and clinical administration of stem cells; and (3) target and kill cancer stem cells while promoting stem cell mediated healing.

WELLNESS IN CHINESE MEDICAL THEORY

While beneficial effects are being documented of herbal medicines combined with chemotherapy—and most recently with immunotherapy—Chinese medical traditions caution against undue use of medicines. The traditional emphasis has been more on a nutritional and lifestyle approach to preventing and managing disease. The 7th Century CE master physician and scholar, SUN Si-miao cautioned in his work *Thousand Golden Essential Prescriptions* (Bei Ji Qian Jin Yao Fang) against the excessive use of medicines. Sun counselled in favour of a healthy diet and lifestyle: 'When a person's body is balanced and harmonious, you must merely nurture it well. Do not recklessly ingest medicinals because the power of medicinals assists only partially and causes the person's visceral qi to become imbalanced, so that they easily contract external trouble'.

SUN Si-miao also offers a bridge into what in the 21st century context is widely referred to as wellness: 'People who practice medicine must first thoroughly understand the source of the disorder and know what has been violated. Then, use food to treat it, and if food will not cure it, afterwards apply drugs.' SUN Si-miao also urged good eating habits, such as thorough chewing, slow swallowing, no overly rich or greasy food, cooking food well, avoidance of cold or raw foods and avoiding excessive drinking. Sun's work is the subject of ongoing scholarly analysis in China.⁽⁴⁹⁾

This approach has been articulated in a contemporary context, including dietary considerations such as seasonal adaptations and varying requirements for children and the elderly.⁽⁵⁰⁻⁵²⁾

In the context of diet and cancer, research published in the Proceedings of the National Academy of Sciences has suggested that inflammation resulting from a molecule introduced through consumption of red meat could promote tumor growth. The molecule, Neu5Gc, is a type of glycan, or sugar molecule, that humans don't naturally produce, but that can be accumulated in human tissues as a result of eating red meat. The body then develops anti-Neu5Gc antibodies – an immune response that could potentially lead to chronic inflammation, and this may contribute to cancer risk.⁽⁵³⁾ Subsequent research from the World Cancer Research Fund and the American Institute for Cancer Research provides suggestive evidence that animal fat intake increases the risk of colorectal cancer.⁽⁵⁴⁾

By contrast, a large population study followed the diets and health of 61,000 participants in Britain over more than a decade. Published in the British Journal of Cancer, the study found that vegetarians—including those who eat fish—are 50 percent less likely to develop some types of cancer than people who eat red meat.⁽⁵⁵⁾ These findings have been contested by a meta-analytic study conducted by a contract research organization in the US, with funding from the Cattlemen's Beef Board, through the National Cattlemen's Beef Association, and the National Pork Board.⁽⁵⁶⁾

In a cross-paradigm interpretation of the concept of inflammation, UCLA's Prof. Ka-Kit Hui, at the 2nd Beijing International Symposium on Integrative Medicine (BISIM 2012), drew on published work from his group to note that isolated components from food plants – e.g. beta-carotene – can actually cause harm in certain contexts. Accordingly, Prof. Hui and colleagues argue for the use of whole foods in accord with Eastern traditions rather than with the current fashion of herbal and nutritional extracts.⁽⁵⁷⁾

In bridging the Western notion of 'inflammation' and the Eastern concept of 'heat' or heatiness, these authors note: "Although inflammation is the body's natural mechanism to heal and fight against infection,

an overactive immune system that results in chronic inflammation is now thought to be the underlying cause of multiple health conditions, including cancer, diabetes, heart disease, and obesity." Inflammation, it is noted, is viewed by Eastern medical theory as "internal heat deriving from the dominance of yang. This heat can result from dysregulation of the internal organs, psychological stress, and heat-producing foods." These would be seen as 'pro-inflammatory foods' in Western terminology.⁽⁵⁸⁾

This helpful paradigmatic bridge – linking concepts from separate traditions into a comprehensible and translational framework – highlights an anti-inflammatory approach deep within Chinese medical traditions. With all that is now known about inflammation and cancer risk, this can be seen as a cancer prevention strategy in its own right.

In terms of longevity and healthy ageing, SUN Si-miao held that the human life-span could be prolonged through correct lifestyle and health practices. He prescribed daily breathing exercises (Qigong), massage and light physical exercise (e.g. Tai Chi and walking) and believed the optimal human lifespan to be a century or more.

In current research, Qigong and Tai Chi have been found to have the following positive health outcomes in common: increased bone density; cardiopulmonary benefits; improved physical function; reduced falls and related risk factors; improved quality of life; patient-reported positive outcomes; improved psychological symptoms; and enhanced immune function.⁽⁵⁷⁾ This last point – enhanced immune function – highlights Tai Chi and Qigong as potentially beneficial additions to integrative cancer immunotherapy, thus warranting investigation as partner therapies to immunotherapy.

The modernization of Chinese medicine in the 20th century has added new scientific understanding to the concepts and methods of Chinese medicine. However, with the emergence of modernized traditional Chinese medicine (TCM), there may have been more emphasis placed on medicine and its delivery by health professionals, than on wellbeing and self-maintenance by members of the public themselves. Beyond TCM, there is also a need for bringing out the philosophies and methodologies of

'Traditional Chinese Wellness' (TCW) – such as those advocated by SUN Si-miao – to create culturally-based lifestyle programs for preventing and managing 21st century diseases.

PERSONALIZED THERAPY AND NUTRITION

The concept of 'personalised' therapy that is gaining traction in cancer immunotherapy has deep roots in Eastern medical theory. Both Chinese medicine and Ayurvedic medicine have a constitutional typology based around the notion of individual differences being clustered into identifiable physiological categories. Recent research supports a genetic basis for both the Ayurvedic^(59,60) and Chinese⁽⁶¹⁾ body-type frameworks.

The science of nutrigenomics aims to understand how genetic variation and epigenetic events alter requirements for, and responses to, nutrients. In the context of this work, there is a growing call for nutrition studies to better identify responders and differentiate them from non-responders on the basis of nutrigenomic or metabolomic profiles. This would allow for greater sensitivity to detect differences between groups, with the result that dietary recommendations could be appropriately targeted – i.e. personalized.⁽⁶²⁾

Hui and the East-West Center team from UCLA note that in Chinese medicine the expression of yin-yang (hot and cold) and the Five Phases (sweet, acrid, sour, bitter, and salty) characterize both the person and the food. Foods are selected on the basis of the individual's pattern – including heat cold and dampness conditions. These are then modified according to environment, season, lifestyle etc.⁽⁵⁶⁾

Personal communications have indicated that in the Chinese medical theory of body types, there may be a prevailing view in academic and regulatory circles in Beijing that there are nine body types; in Shanghai there are held to be seven body types; and at some universities offering Chinese medicine degrees in the UK and elsewhere, five body types are taught, according to the Five Element theory. If personalised nutrition, exercise, and mind-body programs are to be provided according to the principles of Chinese medicine, there is clearly a need for regularisation of this situation.

Just as the WHO-led initiative to standardise

acupuncture resulted in a consensus process that produced a researchable framework for acupuncture points,⁽⁶³⁾ there may well be value in mounting a similar exercise for standardising the theory and application of body types within Chinese medicine to provide a replicable and objective basis for evaluating personalised diet and lifestyle recommendations.

CONCLUSION

In discussing promising new developments in Immunotherapy, Martinez-Forero and colleagues observe that: "The general perception is that the road ahead of us is full of combination clinical trials, which hopefully will bring clinical benefit to our cancer patients at a fast pace."⁽⁶⁴⁾ With this perspective clearly in view, it would seem timely for integrative oncology to begin prioritizing integrative cancer immunotherapy and for researchers to collaborate to create a research agenda that: (a) identifies priority natural products for enhancing the immune response, (b) assists standard immunotherapy to increase its efficacy, (c) creates both the micro- and macro-environments necessary for optimal immunity, and hence for the viability of immunotherapy.

The partnership between Eastern therapeutic approaches and immunotherapy becomes compelling when considered in the light of the following: (1) fewer or no side-effects from immunotherapy, compared with chemotherapy; (2) reduced systemic damage when immunotherapy is chosen over chemotherapy; (3) increased survival of late stage cancer patients when given palliative care rather than aggressive chemotherapy; (4) the compatibility between immunotherapy and Eastern medical concepts – viz. building immunity, prevention, self-care, reducing both site-specific and systemic inflammation, creating balance; (5) commonalities between nutrigenomics, metabolomics and Eastern concepts of individual differences in the profiling of individuals according to genotypes in order to optimize the therapeutic gains of personalised nutritional programs.

A deep examination of Chinese medical theory and clinical practice relating to immunity seems called for. This needs to be supported by a comprehensive research agenda to take immunotherapy from an adjuvant and post-chemo regimen to a front-line treatment. The 'integrative' component will come via partnership with quality-of-life-enhancing and immune-

boosting contributions from time-tested and evidence-based traditional therapies. These, in turn, may yield new sources of immunotherapy in their own right.

If this challenge is taken up in a comprehensive manner, a new paradigm for the prevention, treatment and – hopefully – cure of cancer would seem to be waiting.

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