Wedding Rigorous Scientific Methodology and Ancient Herbal Wisdom to Benefit Cancer Patients: The Development of PHY906

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Figure 1. **PHY906 and Its Four Principal Herbs**—*Glycyrrhiza uralensis* Fisch, *Paeonia lactiflora* Pall, *Scutellaria baicalensis* Georgi, and *Ziziphus jujuba* Mill.

Figure 1. PHY906 and Its Four Principal Herbs

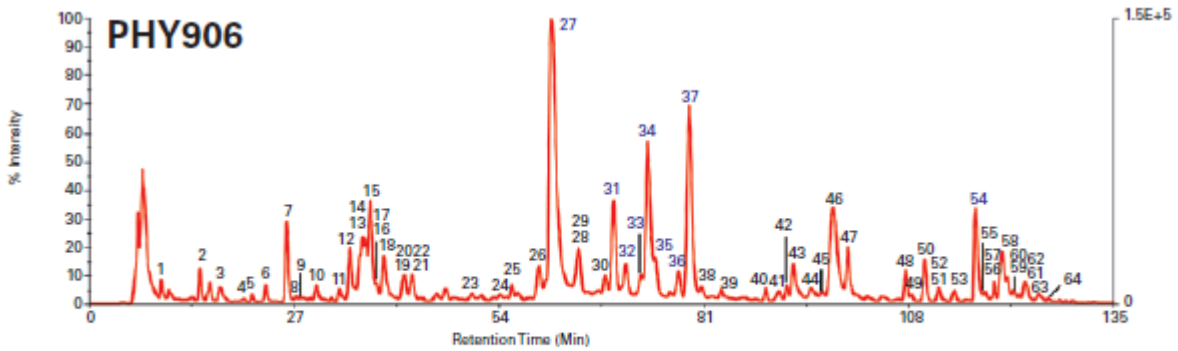

Figure 2. **Chemical Fingerprint Analysis of PHY906 by LC-MS**—Up to 65 individual chemicals have been identified in PHY906 by LC-MS analysis.

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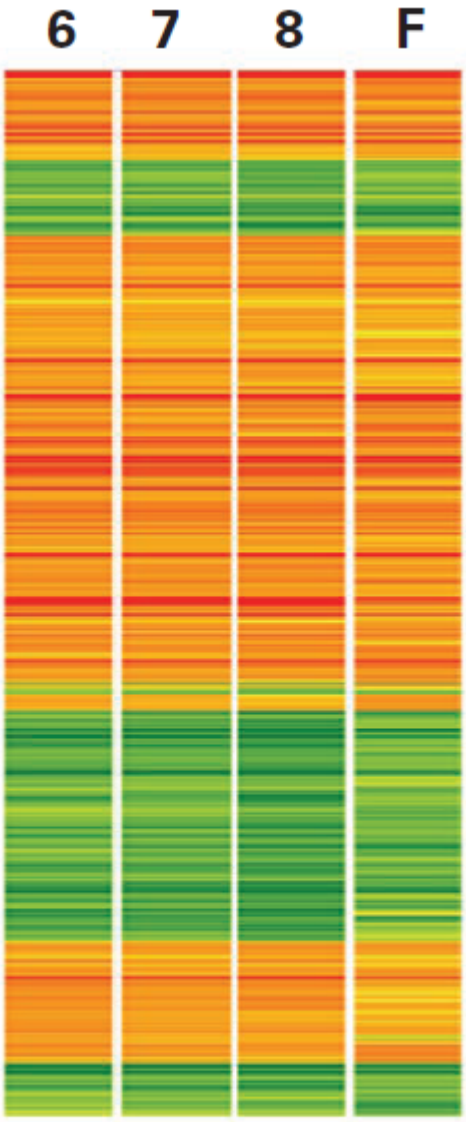

Figure 3. Gene Expression Profiling of PHY906—Lanes 6, 7, and 8 represent batches prepared under Current Good Manufacturing Practices (CGMP) as determined by the US Food and Drug Administration, whereas lane F represents a batch of PHY906 that was not prepared under CGMP guidance.

Figure 3. Gene Expression Profiling of PHY906

Abstract / Synopsis:

Our research group has extensively characterized the preclinical and clinical activities of PHY906, a traditional Chinese herbal medicine, as a modulator of irinotecan-based chemotherapy for the treatment of colorectal cancer. This article reviews the critical issues of quality control and standardization of PHY906 and highlights the importance of high-quality material for the conduct of preclinical and clinical studies. Studies to investigate the potential biological mechanisms of

action using a systems biology approach play a pivotal role in providing the preclinical rationale to move forward with clinical studies. For early-phase clinical studies, translational biomarkers should be incorporated to characterize the biological effects of the herbal medicine. These biomarkers include tumor mutational load, cytokine/chemokine expression, metabolomic profiling, and the presence of key herbal metabolites. Sophisticated bioinformatic approaches are critical for mining the data and identifying those biomarkers that can define the subset of patients who will benefit from PHY906 or any other herbal medicine, in terms of reduced treatment toxicity, improved quality of life, and/or enhanced clinical activity of treatment.

Introduction

Complementary and alternative medicine (CAM) are medical and healthcare practices that are considered outside the realm of conventional mainstream Western medicine.[1,2] Specifically, complementary medicine involves the use of healing practices and products that work together with conventional medicine. In contrast, alternative medicine is used in place of traditional therapies. The National Center for Complementary and Integrative Health (NCCIH; known until 2015 as the National Center for Complementary and Alternative Medicine [NCCAM]) has recognized five main categories of CAM: mind-body medicine; whole medical systems; manipulative and body-based practices; energy medicine; and biologically based practices with a focus on herbal medicines, dietary supplements, vitamins, and nutrition. More recently, the NCCIH has developed the term integrative medicine, which combines conventional medical therapies and CAM therapies in a more highly coordinated and integrated manner based on high-quality evidence of safety and effectiveness. There are many definitions of “integrative” medicine, but all involve bringing conventional and complementary approaches together in a coordinated way. The use of integrative approaches to health and wellness has grown significantly within healthcare settings across the United States.[3]

Over the past 10 to 15 years, there has been steadily increasing use of integrative medicine approaches in conjunction with conventional systemic anticancer therapies.[4-10] It is estimated that 40% to 50% of cancer patients, and perhaps more, have used integrative medicine therapies for symptom relief during the course of their conventional systemic treatments. Acupuncture, for example, has been shown to be an effective mind-body practice in alleviating treatment-associated side effects of fatigue, postoperative pain, and nausea and vomiting.[11-15] An important medicinal agent in cancer care is ginger (Zingiber officinale), a flowering plant whose rhizome is widely used as a folk medicine, and which is available in a variety of formulations. Ginger supplementation may represent an alternative adjuvant treatment for chemotherapy-induced nausea and vomiting. Controlled randomized clinical trials to confirm the clinical benefit of ginger are ongoing.[16,17] Finally, integrative medicine approaches have become especially popular with cancer survivors to manage the adverse effects and consequences of particular treatments —whether they be surgical resection; radiation therapy; or systemic therapy with cytotoxic chemotherapy, targeted therapy, and/or biologic therapy.

Chinese Herbal Medicine and the Herbal Formula PHY906

Traditional Chinese medicine has been practiced for more than 2,000 years. The earliest medical text on traditional Chinese medicine, written around 200 AD, includes the medicinal and toxicological properties of 364 entries, the vast majority describing plants.[18] In the 16th century, the classical Chinese herbal medicine textbook documented the use of nearly 1,900 individual herbs and more than 11,000 formulas to treat human diseases.[19] Traditional Chinese medicine has been used to control disease-associated symptoms and to improve overall quality of life for patients affected by a wide range of medical conditions, including cancer, gastrointestinal disorders, skin disorders, fatigue, stress, liver disease, cardiovascular disease, and allergies and autoimmune diseases.

Our own studies of traditional Chinese medicine began in the early 2000s, when we sought to answer the question of whether there was a Chinese herbal medicine that could prevent and/or reduce the gastrointestinal toxicities associated with irinotecan-based chemotherapy. Around that time, the combination of irinotecan, fluorouracil (5-FU), and leucovorin (IFL) was being developed as a frontline treatment regimen, and it was associated with a 25% to 30% incidence of grade 3 or 4 gastrointestinal toxicity in the form of diarrhea, nausea and vomiting, and abdominal cramps. Two large phase III clinical studies sponsored by the National Cancer Institute revealed an increased early death rate in patients treated with the IFL regimen, which was largely secondary to the treatment-related gastrointestinal toxicities. With this in mind, Professor Yung-Chi Cheng, PhD, and his research team at Yale University reviewed the Chinese literature and identified Huang Qin Tang as a classic formula that has been widely used in China and other Asian countries to treat gastrointestinal disorders, including nausea and vomiting, abdominal cramps, and diarrhea,[19,20] with the latter presumably occurring secondary, but not limited to, infectious etiologies in humans without serious side effects, other than reversible constipation.

PHY906 is a powder containing a spray-dried aqueous extract derived from the Huang Qin Tang formula; it consists of four principal herbs (Figure 1): *Glycyrrhiza uralensis* Fisch, *Paeonia lactiflora* Pall, *Scutellaria baicalensis* Georgi, and *Ziziphus jujuba* Mill. Of note, up to 65 individual chemicals have been identified, to date, in these four herbs. The identity of each herb was confirmed by trained botanists, and the plants were closely monitored with respect to soil and growth conditions to ensure the highest levels of chemical consistency in the raw herbs. In addition, testing was performed to ensure the absence of contaminants, such as heavy metals, pesticides/insecticides, and various microbial organisms. In contrast to Huang Qin Tang, the PHY906 formulation was prepared according to a proprietary manufacturing protocol that was specifically designed and implemented by Sun Ten Pharmaceutical Company in Taiwan. This protocol employed standard operating procedures involving hot water extraction of the four herbal components in a specific dry weight ratio of 3:2:2:2; this ratio is different from that which is traditionally used in everyday clinical practice in Asia. The hot water extraction was then spray-dried into a granulated powder and packaged in the form of capsules according to stringent manufacturing practices that followed Current Good Manufacturing Practices (CGMP) as determined by the US Food and Drug Administration.

Quality Control in the Production of PHY906

One of the main challenges associated with the development of Chinese herbal medicine relates to the issue of quality control and batch-to-batch variability. Since herbal extracts contain up to hundreds of individual phytochemical components, it is critical to develop robust quality-control metrics. To address this concern, a platform termed PhytomicsQC was developed; this unique and comprehensive set of methodologies integrates chemical analysis, bioresponse analysis, and in vivo animal pharmacology to achieve quality control and batch-to-batch reproducibility in the production of PHY906.[21] For chemical analysis, liquid chromatography/mass spectrometry (LC/MS) was selected (Figure 2), given its broad capability and increased spectral sensitivity. Gene expression profiling, as seen in Figure 3, was used for bioresponse fingerprinting, since it provides a sensitive, comprehensive, and unique pattern in response to exposure to a given herbal formula. Working closely with Professor Hongyu Zhao, PhD, his bioinformatics colleagues at Yale, and PhytoCeutica (the developers of PhytomicsQC), a Phytomics Similarity Index (PSI) was developed for both the chemical analysis and the bioresponse fingerprint analysis. This PSI value is determined by integrating peak patterns, peak ratios, and peak intensities from various batches; it is a quantitative measure of similarity between two compounds, ranging from 0 to 1, with 1 being identical. This work has been critically important both for the clinical development of PHY906 and as a framework for the development of herbal medicines, as it has shown that herbal formulations manufactured under strict CGMP guidance can yield highly consistent batches of high-quality herbal products that can then be used for both preclinical and clinical studies.

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