

Integrative oncology: evidence-based medicine – The multidisciplinary experience of the Integrative Medicine Research Group (IMRG)

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Abstract. – The purpose of this conference was to explain the relationship between the integrative and complementary medicine and cancer disease through evidence-based medicine. The topics covered are numerous and are characterized by the multidisciplinary approach of the researchers involved in this complex scenario. The Integrative Medicine Research Group (IMRG) studies the complementary and integrative approach in cancer patients with the aim to highlight the risk of drug and nutraceutical and, at the same time, improve the quality of life in this particular set of patients. Our auspicious is to have an integrative medicine approach to all chronic diseases, oncological included.

Key Words:

Cancer disease, Patients, Treatment, Medicinal mushrooms, Integrative oncology, Interactions.

Introduction

The Integrative Medicine Research Group (IMRG) presents here a new conference scene on the role of complementary and integrative medicine (CIM) in the management of cancer patients.

According to the National Center Institute of USA for Complementary and Integrative Health (NC-CIH)¹, integrative medicine is an approach to medical care that combines traditional medicine (TM) with Complementary and alternative medicine (CAM) practices, which has shown safety and benefits as in addition to traditional cancer treatment²⁻¹⁰. This approach often emphasized the patient's preferences

and attempts to address the mental, physical, and spiritual aspects of health. CAM remedies include a wide range of practices and products, whether biological (e.g., herbal products or botanicals, vitamins, minerals, probiotics, homeopathic products, and Chinese herbal remedies) or non-biological (e.g., prayer, meditation, music therapy, yoga), divided into five categories as described in Table I.

It is known that about half of cancer patients already combine CAM remedies with oncological treatments without informing their physician²⁻⁴ and this aspect represents a critical issue for the clinical management of patients.

This conference scene in Milan, launched by IMRG, focuses on the role of CIM in the management of cancer patients in the context of a multidisciplinary and innovative approach.

Oral Session

Cordycepin: Molecular Mechanisms in Oncology

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Cordycepin (3'-deoxyadenosine) acts as an adenosine analog, which is isolated from the caterpillar fungus, *Cordyceps militaris* and *sinensis*, a popular health food and traditional medicine in China¹¹.

Table I. CAM categories according to NCCIH.

CAM categories	Mind-Body therapies	Biologically based practices	Manipulative and body-based practices	Biofield therapy	Whole medical systems
Meditation	✓	×	×	×	×
Biofeedback	✓	×	×	×	×
Hypnosis	✓	×	×	×	×
Yoga	✓	×	×	×	×
Tai Chi	✓	×	×	×	×
Vitamins	×	✓	×	×	×
Dietary Supplements	×	✓	×	×	×
Botanicals	×	✓	×	×	×
Herbs	×	✓	×	×	×
Special foods or diets	×	✓	×	×	×
Massage	×	×	✓	×	×
Chiropractic therapy	×	×	✓	×	×
Reflexology	×	×	✓	×	×
Reiki	×	×	×	✓	×
Therapeutic touch	×	×	×	✓	×
Ayurvedic medicine	×	×	×	×	✓
TCM*	×	×	×	×	✓
Homeopathy	×	×	×	×	✓
Neuropathic medicine	×	×	×	×	✓

*TCM: Traditional Chinese medicine.

Recent studies¹² have reported that cordycepin extracted from *Cordyceps* exhibit multiple physiological functions, and significant therapeutic effects, such as anti-inflammatory and anti-oxidative activity, immune system activation, sexual performance enhancement, anticancer effects, and anti-metastatic effects. This interest has led to a sharp increase in the number of publications on cordycepin as a bioactive compound and potential medicine, which has been particularly strong over the past decade.

Cordycepin has been widely recognized for its therapeutic potential against many types of cancers. In particular, cordycepin can inhibit growth and proliferation, induce apoptosis, disrupt cell cycle, and has cytotoxic effects on cancer cell lines *in vitro*. In addition, cordycepin can induce autophagy, modulate the immune system, and inhibits tumor invasion and metastasis¹³. Several scholars¹³ demonstrate cordycepin is able to overcome multidrug resistance and sensitize tumor cells to chemotherapy and radiotherapy. The molecular mechanisms of action described for cancer prevention and treatment are multiple.

First, one of the main modes of cordycepin action in mammalian cells is the inhibition of 3' end processing of mRNAs (polyadenylation inhibition). It reduces the poly(A) tail lengths of inducible mRNAs, thus preventing their translation in the cytoplasm and inhibiting inflammation¹⁴.

Cordycepin has also been reported¹³ to activate AMP-activated protein kinase (AMPK). AMPK is a highly conserved sensor of low intracellular ATP levels that is rapidly activated after nearly all mitochondrial stresses. It redirects metabolism based on changes in the ATP-to-AMP ratio, regulates autophagy and mitophagy by activating Unc-51 Like Autophagy Activating Kinase 1 (ULK1), enhances mitochondrial dynamics (fusion/fission), and stimulates mitochondrial biogenesis¹⁵. Most of the effects of cordycepin are thought to be mediated by the following mechanism.

Cordycepin inhibits mTOR in cancer cells and suppress tumor growth *in vitro* by inhibiting the mTOR (PI3K/AKT/mTOR) signaling pathway without affecting healthy and non-cancerous cells. The PI3K/AKT/mTOR pathway regulate biological processes such as metabolic balance, growth, differentiation, cell migration and angiogenesis and plays an important role in cancer and many other chronic metabolic diseases. The effect of cordycepin on mTOR activity is usually assessed by inactivation of Akt (phosphorylation) and activation of S6 kinase (S6K), which phosphorylates mTOR and leads to its inactivation¹⁶.

Cordycepin also inhibits the activation of NF- κ B, a transcription factor that plays a key role in activating genes during inflammation. The effects of cordycepin on NF- κ B-mediated transcription

occur at multiple levels and are somewhat variable, probably depending on which combination of gene, cell type, and stimulus studied, but the final result is a reduction of the inflammatory response and of cancer progression.

It is clear from the literature that cordycepin has an anti-proliferative and anti-inflammatory effect and regulates apoptosis, cell survival, growth, and division of cancer cells. It also reduces migration, invasion, and metastasis by decreasing the expression of matrix metalloproteinases (MMP) and up-regulating the epithelial marker E-cadherin, suggesting a reversal of the epithelial-to-mesenchymal transition¹⁶.

Studies¹⁶ of combination therapy show a synergistic effect of cordycepin and chemotherapy (paclitaxel, mitoxantrone, gemcitabine, cisplatin, 5-FU, TKI, temozolomide, and others) and a higher sensitization of cancer cells to chemotherapy. Cordycepin appears to attenuate multidrug chemoresistance and improve cytotoxicity¹⁷. It also sensitizes cancer cells to radiation but prevents radiation damage in healthy tissues by inhibiting cell senescence *via* nuclear factor erythroid 2-related factor 2 (NRF2) and AMPK in rodents¹⁸.

Recently a phosphoramidate transformation of cordycepin has been used to develop a drug (ProTide NUC-7738) to enhance the activity of cordycepin. Phase I/II studies¹⁹ are ongoing, and the results are promising since the drug is well tolerated and shows clinical effectiveness.

Natural compounds such as cordycepin, their synthesis, and their activities surely are promising sources for new research in the field of CAMs.

Although cordycepin is the compound influencing several metabolic pathways involved in tumor growth and metastasis, its activity is thought to be due to the synergy of the fungal mixture rather than the single molecule. In terms of integrative use, cordycepin-rich Cordyceps may be the best choice for integrative use in cancer.

Evaluation of In Vivo Effects of a Medicinal Mushroom Mixture on a Preclinical Model of Triple-Negative Breast Cancer

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Medicinal mushrooms have been part of traditional Chinese medicine for centuries and are particularly used in the treatment of various

pathologies thanks to their immunomodulatory, antioxidant, anti-inflammatory, and anticancer properties²⁰. Micotherapy is an expanding field that needs caution, both in terms of safety and efficacy: *in vitro* and *in vivo* studies are needed to validate the presumed pharmacological effects of these mushrooms, and to avoid side effects derived from their use²¹. A recent work provided data supporting the alleged anticancer properties of a mixture of mushrooms (*Agaricus blazei*, *Ophiocordyceps sinensis*, *Ganoderma lucidum*, *Grifola frondosa*, and *Lentinula edodes*) in a mouse model of triple-negative breast cancer (TNBC). The mixture named “Micotherapy U-care” caused a decrease of oxidative stress and inflammatory pathways, reducing the expression pattern of interleukin-6 (IL-6), nitric oxide synthase 2 (NOS2), and cyclooxygenase-2 (COX2) in murine lung tissue, which is highly at risk of metastasis in primary mammary carcinoma²². These effects are related to the reduction of pulmonary metastases density and reduced fibrotic response. The obtained results potentially promote the use of this mixture in improving the quality of life of patients suffering from TNBC, even if further investigations and clarity are needed to convert these data into an appropriate clinical treatment plan.

Risks and Benefits of Concomitant Use of Herbal Products and Anticancer Drugs in Complementary and Alternative Medicine

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Complementary and alternative medicine (CAM) therapies include a wide range of procedures and products often used by cancer patients to directly counteract cancer and protect normal cells from the toxic effects of conventional therapies²³. Unfortunately, self-prescription of natural remedies in cancer patients can lead to unexpected toxicities and can reduce the effectiveness of cancer therapy. Although CAM usually refers to any “natural or organic” products/methods that are generally considered less toxic, there are concerns about drug interactions, mainly because

CAM lacks clear scientific evidence of safety and efficacy²⁴. Drug-Herbal product association may result in the altered pharmacokinetics of one or both active agents and/or altered pharmacodynamics, affecting their efficacy, especially the positive outcome of drug therapy²⁵. Metabolic interactions may alter the amount of the drug that reaches the target site, resulting in either therapeutic inefficacy or even toxicity due to an overdose. The induction/inhibition of cytochromes P450 (CYPs) and interaction with P-glycoprotein are the main ones responsible for this kind of problem^{26,27}. On the other hand, it should be emphasized that natural products can be adjuvant in various pathologies, reducing the side effects deriving from the use of anticancer drugs or synergizing their action. The use of a natural product must therefore be optimized according to the administered anticancer therapy minimizing side effects deriving from interactions and creating highly safe personalized therapeutic plans.

Clinical Experience About the Use of Complementary and Alternative Medicine in Spain

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It is estimated that the frequency of use of complementary and alternative medicine (CAM) in Spain is very similar to that in other European countries.

Although there are no official data, it is estimated that more than 60% of patients use these therapies, mostly on their own prescription and without informing their oncologist. The most commonly used CAMs are biological (mainly phytotherapy) and body-mind techniques, ahead of homeopathy and oriental medicine²⁸.

Today there is a growing demand for this type of therapy and for the so-called “personalized treatments”. This reality implies that oncologists must be scientifically trained to adequately counsel their patients²⁹.

The World Health Organization (WHO) itself, in its document “Strategy 2014-2023”, considers that CAMs are a right to which patients should have access. To this end, it defines the ethical principles (patient and professionals are partners in the healing process), the rights of the patient (receiving adequate and up-to-date information, and safe treatment in oncology), the obligations of the patient (reporting the health status), the

rights of physicians practicing CAM must be respected by professional associations, among others, and the obligations of all health professionals³⁰.

The principle of paternalistic medicine, typical of the twentieth century, is today replaced by the principle of patient autonomy in medicine, according to which the patient, duly informed, decides on his treatment.

In Spain, there are currently several public and private initiatives that are tentatively giving cancer patients access to these therapies. Of note are the Spanish Society of Integrative Medicine (SESMI), which offers courses, congresses and training and has recently published a treatise on Integrative Oncology, and the Association of Integrative Oncology, which provides support to patients on various topics (nutrition, lifestyle, forms of therapy). Among public hospitals, the San Juan de Dios Children’s Hospital in Barcelona stands out, which has promoted the creation of a special department of integrative oncology for children with cancer. This activity does not involve any additional cost for patients, as it is financed by private donations. The most commonly used treatments are acupuncture and aromatherapy. In addition, Hospital Clínico de Barcelona was a pioneer in introducing mycotherapy (Dr. Gascón) for cancer patients. However, this initiative was discontinued despite promising results³¹.

The discontinuation of this service faces the current situation in Spain regarding the use of CAM in oncology: the legal framework of action for health professionals (rights and obligations), the public and private initiatives that promote their use, the responsibility of conventional oncologists, and the importance of raising patients’ awareness of the need to communicate the use of CAMs to their physicians.

In this conference, some clinical cases of patients successfully treated with mycotherapy will be presented, where not only an improvement in the quality of life but also a good evolution of the disease (in terms of reduction of metastases and size of cancer) has been observed.

In conclusion, CAM is slowly being implemented in the field of oncology in Spain, with greater acceptance in private centers than in public hospitals. There is a growing demand for this type of integrated approach from both patients and physicians, who want adequate and up-to-date training in this field.

In summary, CAMs integrate conventional

cancer therapies without ever replacing them, suggesting that they can help improve patients' QoL and reduce side effects.

Physical Activity and Phytotherapy as Tools to Fight Osteosarcopenia in the Cancer Patient

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Sarcopenia and osteopenia are two conditions that characterize the progression of cancer, both as a direct effect of the disease on the body and as a typical feature of aging³². About 60% of cancer cases occur after the age of 65, when the susceptibility of the organism increases, as well as the occurrence of toxicity in cancer patients receiving chemotherapy. Sarcopenia, which is the progressive and general loss of skeletal muscle, mass and strength, as well as the level of physical performance, has a negative effect on the general health of the individual. Sarcopenia has also been associated with low bone mineral density (BMD); a condition known as osteopenia. This suggests that low muscle mass reduces the mechanical load on the skeleton, resulting in reduced bone formation. The two conditions often occur together and are defined by a single term: osteosarcopenia.

To date, osteosarcopenia was found to be a negative prognostic factor for patients undergoing liver resection for colorectal liver metastases (CRLM)³³. Among patients with osteosarcopenia, women were predominant and body mass index (BMI) was lower compared with patients without osteosarcopenia.

Osteosarcopenia is treated nutritionally with protein supplementation and/or vitamin D and calcium, which are certainly necessary supplements in the case of an identified deficiency. Today, however, another decisive factor for the causality of these two diseases has emerged, namely the inflammation³⁴.

In osteosarcopenia, which is typical of the elderly, there is often a concomitant increase in chronic inflammation, the causes of which are often related to lifestyle, poor diet, lack of exercise, chronic stress, obesity, xenobiotics, and so on. Physical activity is a valid, as well as effective, method for preventing and improving the conditions of osteosarcopenia. Depending on the age of the subject and the clinical condition, important

combined work strategies can be applied: aerobic, anaerobic and stretching training, with the aim of maintaining and improving both muscle mass and bone remineralization through mechanical stimuli and through the anti-inflammatory effect of physical exercise³⁵.

Another important tool for treating the inflammatory aspect is undoubtedly herbal medicine. Plants with anti-inflammatory activity such as *Curcuma Longa* and *Boswellia Serrata*, when used in phytosomal form, have a low impact on pharmacokinetics and are therefore compatible with cancer therapies³⁶. In addition, *Curcuma Longa* helps to sensitize cancer cells to chemotherapy and protect normal cells from the damage caused by chemotherapy as well as mitigating the side effects of chemotherapy itself³⁷.

Improved Survival and Quality of Life Through an Integrative and Multidisciplinary Oncology Approach: Preliminary Results on Four Clinical Cancer Patients

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According to the National Cancer Institute, the integrative medicine (IM) approach to medical care that combines standard medicine with CAM practices is proved to be safe and effective³⁸. In this study, we described the preliminary results of using an IM approach in four patients with malignant pleural mesothelioma (MPM), diffuse malignant peritoneal mesothelioma (DMPM), intrahepatic cholangiocarcinoma, and breast cancer (BC), respectively, who received supportive treatment (ST) according to an IM approach after the failure of standard cancer therapies or the occurrence of serious adverse events due to antineoplastic chemotherapy. The ST consisted in supplementation with Vitamin C, Vitamin D, probiotics, and a blend of medicinal mushrooms. The crucial role of IM in reducing the adverse events (AEs) of cancer therapies and improving Health-related Quality of Life (HR-QoL) in cancer patients has already been demonstrated⁵. The IM approach was well tolerated, and no serious AEs occurred. In addition, IM improved the HR-QoL and cancer related fatigue in all patients³⁹. Additionally, in two cases (MPM and DMPM) a significant exten-

sion of overall survival was obtained and in one case (BC) a complete hematological recovery. No interactions between IM and target therapy were observed in BC patients. Our IM approach consisted in a combination of TM and CAM which resulted in a safe and effective strategy. The 4 clinical cases herein described, provide typical examples of an IM approach that was conceived by a multidisciplinary team and shared with the patients. The extended clinical and instrumental response of patients with MPM and DMPM to IM, as well as the improved HR-QoL and good tolerability of the ST, demonstrated in all cases, support the value of this approach in patients whose cancer therapies have failed and who have a good performance status⁵. Of course, our data need to be confirmed in a well-designed prospective clinical trial.

Prescriptions Appropriateness in Biological Cams' User

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Drug-drug/drug-herbs interactions can affect both the pharmacokinetics and pharmacodynamics of drugs leading to adverse reactions development or enhancing the drug's activity in a synergistic manner. Several factors may influence the risk of these types of interactions, including the use of concomitant drugs and the presence of co-morbidities that typically characterize elderly patients⁴⁰. Commonly, most patients diagnosed with cancer are already affected by one or more diseases and are administered one or more therapies. In addition, chemotherapy involves the use of several antitubercular drugs with cytotoxic effects along with drugs that support chemotherapy and drugs that are intended to relieve the symptoms of the chemotherapy itself. For this reason, in the cancer patient, especially if elderly, the evaluation of drug-drug/drug-herbs interactions becomes crucial in order to avoid the ineffectiveness of the therapy or the development of serious toxicities that are potentially harmful and may require hospitalization⁴¹. Patients' use of herbal supplements and remedies very often remains hidden from physicians, and, on the other hand, physicians have little knowledge of biological CAMs. Despite the existence of different tools able to check the risk of interactions between

drugs and/or herbal remedies, their use is very limited in the current clinical practice. Some of these checker programs, including Lexicomp, Medscape, and Micromedex, have databases that include drugs and several commonly used herbs and can analyze and classify the risk of interactions in accordance with evidence-based scientific data⁴²⁻⁴⁴. Ideally, the cancer patient's journey may include an assessment of the risk of interactions between chronic drugs, supplements and/or herbal remedies, and chemotherapy drugs that will be administered to the patient. Moreover, these programs may be useful to assess the causality relation between drugs and/or herbs whenever an unexpected adverse reaction occurs during the therapies enabling their adjustment or modification. These assessments are also needed when an herbal remedy is prescribed by a physician aiming to improve the patient's HR-QoL in order to enhance the prescription appropriateness and safety⁴⁵. This ideal routine requires not only the knowledge of these programs and their implementation in clinical practice but also the dissemination of basic knowledge about biological CAM (Figure 1). In addition, the disclosure of CAMs' benefits and risks among healthcare personnel may encourage patients to inform their physicians about the self-prescribed herbal remedies, overcoming the sense of shame that very often accompanies this type of information. In addition to the need to spread the knowledge of CAM among healthcare professionals, several obstacles need to be overcome by integrating the checker program databases with a wider range of organic

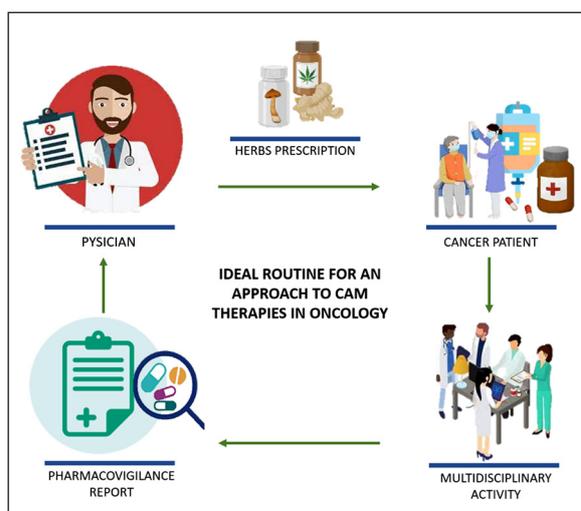


Figure 1. Ideal multidisciplinary approach for CAMs prescription into the cancer patient journey.

herbs and CAMs, training staff on the use of these programs and introducing university-level integrated oncology courses for the professionals of tomorrow⁴⁶. In addition, the in-depth knowledge of drug-herbal interactions that characterize the role of pharmacists/pharmacologists should be used at the clinical level to promote an effective pharmacovigilance model.

In particular, in the field of oncology, interdisciplinary networks between oncologists and pharmacists/pharmacologists could review the appropriateness and safety of pharmacologic and integrative prescribing in patients exposed to highly toxic antineoplastic treatments and already having chronic diseases under treatment.

Conclusions

The IM plays a key role in the treatment of cancer patients, and this type of approach should be shared by physicians and patients⁴⁷.

Unfortunately, physicians' lack of knowledge about CIM and their limited communication with patients have negative consequences and impacts on clinical management and outcomes⁴⁸. In addition, it has been demonstrated⁴⁹ that the use of alternative medicine instead of CM and from the CIM approach was associated with worse five-year survival in cancer patients.

Considering that more than half of cancer patients use CAM without medical indication, the risk of drug-herbal interactions is high^{23,50}.

Moreover, the use of CAM is also common in patients with chronic diseases or chronic symptoms⁵¹⁻⁵⁸ as described in the English literature.

In conclusion, we believe and hope that the CIM approach within a multidisciplinary team is a valid option to improve HR-QoL in cancer patients, chronically ill patients, and so-called frail patients⁵⁹⁻⁶².

In the near future, we would like to propose and organize prospective studies within the IMRG to improve knowledge about different categories of patients treated within a multidisciplinary and integrative approach. Scientific and practical information about integrative medicine in cancer patients is described in Table II.

Conflict of Interest

Dr. Pier Paolo Zanello, Dr. Daniele Santagà and Dr. Stefania Cazzavillan are scientific consultants for AVD Reform.

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Table II. Reputable resources for information about Integrative Medicine and Complementary Therapies in cancer settings.

<p>American Cancer Society: Guidelines for Using Complementary and Alternative Methods (available at: http://www.cancer.org/Treatment/TreatmentsandSideEffects/ComplementaryandAlternative).</p> <p>Medline Plus (available at: http://www.nlm.nih.gov/medlineplus/druginfo/herb_All.html).</p> <p>Memorial Sloan-Kettering Cancer Center (MSKCC) About Herbs, Botanicals and Other Products (available at: http://www.mskcc.org/aboutherbs and www.MSKCC.org/IntegrativeMedicine).</p> <p>National Cancer Institute: Topics in Complementary and Alternative Therapies (PDQ) (available at: http://www.cancer.gov/cancertopics/pdq/cam/topics-in-cam/health_professional).</p> <p>National Center for Complementary and Alternative Medicine (NCCAM) (available at: http://nccam.nih.gov/health/cancer/camcancer.htm).</p> <p>NCCAM Time to Talk Toolkit: Ask Your Patients About Their Use of Complementary Health Practices (available at: http://nccam.nih.gov/time_to_talk/forphysicians.htm).</p> <p>NIH Office of Dietary Supplements (available at: http://ods.od.nih.gov/).</p> <p>Society for Integrative Oncology (available at: http://www.integrativeonc.org/).</p> <p>United States Pharmacopeia (USP) Dietary Supplement Standards (available at: http://www.usp.org/dietary-supplements/overview).</p> <p>Abrams D, Weil A. Integrative Oncology. Oxford University Press, 2009.</p> <p>Cassileth B. The Complete Guide to Complementary Therapies in Cancer Care: Essential Information for Patients, Survivors and Health Professionals. Wspc, 2011.</p> <p>Cassileth B. Survivorship: Living Well During and After Cancer. Spry Publishing, 2014.</p> <p>Ernst E, Pittler MH, Wider B. The Desktop Guide to Complementary and Alternative Medicine: An Evidence-Based Approach. Mosby Ltd, 2006.</p>

Scientific Manager of the Event

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