Takeo Wada Cancer Research Symposium in Chiang Mai

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In 1984, the Ministry of Education, Science and Culture in Japan founded the Overseas Scientific Research Survey (Cancer Program) in collaboration with cancer researchers of various Asian nations. The first Chairman, Dr. Kunio Aoki, President of Aichi Cancer Center at that time, strongly encouraged young Japanese scientists to initiate research projects with new ideas and thoughts. Subsequently, a collaboration commenced between Drs. Maitree Suttajit and Vichai Wongchai at the Department of Biochemistry, Faculty of Medicine, Chiang Mai University, and Dr. Hirota Fujiki at the National Cancer Center Research Institute in Tokyo, later at Saitama Cancer Center Research Institute, where he was joined by Dr. Kei Nakachi. Our collaboration and our professional friendship were valuable in organizing this meeting.

Thanks to Prof. Wada

Prof. Takeo Wada, formerly President of Sapporo Medical University and an internationally respected leader in medicine, continuously encouraged young Thai scientists. And he and Mrs. Wada, beginning in 1986, made periodical financial contributions to the Faculty of Medicine, Chiang Mai University. The generosity of the Wadas has been a prime factor in the great success of our scientific collaboration. Therefore, when scientists in Chiang Mai originally planned to organize an International Symposium, they decided to name it the Dr. Wada Memorial Symposium, to celebrate the spirit of Prof. Wada’s cosmopolitan cancer research. Prof. Wada, however, took exception to the proposed title, and Thai scientists yielded to Prof. Wada’s modesty, so the event was named the Thai-Japan Cancer Research Symposium, with the first held at Chiang Mai University on November 5–6, 1998. A second symposium was anticipated in Chiang Mai, 2000, but another change in the name of the symposium was to be made: Prof. Wada was taken from us by a sudden heart attack in Chiang Mai, his favorite city, on January 30, 1999. Whereupon, scientists of both nations unanimously agreed to name the second symposium the Takeo Wada Cancer Research Symposium. This was held at Chiang Mai University on November 30 and December 1, 2000, and we present here our Meeting Report as one of the representative successful outcomes of projects from the Overseas Scientific Research Survey (Cancer Program).

Memorial lectures

The special session included three lectures in memory of Prof. Wada and the newly established Takeo Wada Award lecture for young Thai scientists, at the beginning of the Symposium. The three memorial lectures, by Prof. Wada’s daughter Dr. Sato Honma, Dr. Kohzoh Imai and Dr. Maitree Suttajit, were a highlight of this symposium. Dr. Honma, Professor of the Physiology Department at Hokkaido University Graduate School of Medicine, studied medicine as her father had, but she then went into basic medical research, studying circadian rhythms. In her lecture she spoke on the roots of her father’s motivation for his own international medical exchange program between Japan and more than 14 developing countries in East Europe, the Middle East and Asia as follows: after his graduation from the School of Medicine in 1940, he became a naval medical officer on the aircraft carrier “Hiryu” during the period from Pearl Harbor to Midway. Prof. Wada’s experience during World War II and his feeling of responsibility as a survivor led him to help people in many countries by teaching medicine and introducing new medical technology. Chiang Mai was one of his favorite places.

Dr. Imai, Professor of the First Department of Internal Medicine, Sapporo Medical University, was asked by Prof. Wada to be his successor, in order to carry on the spirit of Prof. and Mrs. Wada’s friendship to the next generation in Chiang Mai. Dr. Wada in collaboration with the late Dr. Hidematsu Hirai established the International Society for Oncodevelopmental Biology and Medicine (ISOBM) in 1973, and ISOBM has held annual international meetings since then. This was the beginning of translational research between basic cancer research and clinical application in Japan. Dr. Imai reported on his ISOBM project: molecular studies on the role of matrix metalloproteinase (MMP)-7, matrilysin, in the progression of colorectal adenocarcinoma and esophageal squamous cell carcinoma.

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Dr. Maitree Suttajit, who established the Dr. Wada Cancer Research Fund at Chiang Mai University, recalled happy days of academic visits with his mentor Prof. Wada and Mrs. Yuriko Wada in Thailand, Laos, Indonesia, Vietnam and Japan. Drawing on his personal experience, Dr. Suttajit eloquently spoke of Prof. Wada as a real doctor and kind teacher for people in different countries, showing how deeply one person can influence and educate students, and how greatly he devoted himself to helping others throughout his life. Dr. Suttajit’s lecture, entitled “In Memoriam: Professor Dr. Takeo Wada,” is included in the abstract of this Symposium. It is a beautiful story of mutual respect between two families and between mentor and pupil.

Award lecture

This year, the Dr. Wada Cancer Research Fund and the Faculty of Medicine, Chiang Mai University, established the Prof. Wada Award, consisting of a plaque and 30,000 bahts (about $1,000), for young Thai scientists who have made a substantial contribution to cancer research. The first Award was presented to Dr. Apiwat Mutirangura, Associate Professor of Genetics Unit, Department of Anatomy, Faculty of Medicine, Chulalongkorn University, by Mrs. Wada and Dr. Piya Netrawichien, Dean, Faculty of Medicine, Chiang Mai University.

Dr. Apiwat’s Award lecture, entitled “Molecular Mechanisms of Nasopharyngeal Carcinoma Development,” was another highlight of the morning. He raised the question of why nasopharyngeal carcinoma (NPC) is found most frequently in Chinese individuals—especially in the southern part of China, while infection of Epstein-Barr virus (EBV) as an etiologic factor is distributed worldwide. Based on molecular studies with EBV, Dr. Apiwat reported many new findings: involvement of EBV in lymphoma in Thailand, detection of EBV DNA in serum of NPC patients and its clinical application as a promising tumor marker, and genetic alterations and loss of heterozygosity in NPC. All participants congratulated Prof. Apiwat as the first awardee, and his lecture demonstrated that he is a highly competent young scientist with a well-deserved international reputation. We also felt that Prof. Wada, looking down from heaven, smiled on Prof. Apiwat’s superb presentation.

Cancer prevention

Participants were aware from the Abstract that the goal of the symposium was to disseminate news on advancements of cancer research in such areas as carcinogenesis, diagnosis, prevention and treatment. The Symposium provided an excellent opportunity to exchange knowledge and experience, and also to create friendships in an academic atmosphere. Sixteen oral presentations on three themes—cancer prevention, cancer treatment and molecular mechanisms of cancer—were given by scientists from 13 institutions (9 Japanese, 3 Thai, 2 US, 1 Czech Republic and 1 UK), along with 17 poster presentations. More than 200 people took part during the 2 days.

Among the most notable speakers was Dr. Floyd W. Dunn, Visiting Professor, Department of Biochemistry, Chiang Mai University. Dr. Dunn has created a long and valuable friendship with Thai scientists in Chiang Mai University, a friendship that goes back to Dr. Dunn’s work as a member of the University of Illinois College of Medicine—Chiang Mai Project, 1965–1968. In his presentation, Dr. Dunn, as a Visiting Professor, strongly recommended introducing cancer prevention into medical education, based on his world-wide knowledge and extensive study on the latest cancer research. He noted that “putting cancer prevention into medical education” was accepted as a new project at Baylor College of Medicine in Houston last year.

Dr. Hisataka Moriwaki, First Department of Internal Medicine, Gifu University School of Medicine, clearly demonstrated that the development of second primary cancer after curative treatment for preceding hepatocellular carcinoma could be prevented by one year administration of a synthetic analog of vitamin A, acyclic retinoid, or 4,5-dehydro-geranylgeranoic acid, and that this sustained preventive activity provided a good prognosis for cancer patients five years after its administration. Dr. Moriwaki discussed the preventive mechanism using the concept of clonal deletion of premalignant and latent malignant cells. Since liver cancer is common in Asian countries, Thai scientists showed strong interest in the cancer preventive effects of the compound, acyclic retinoid.

Dr. Kei Nakachi, Saitama Cancer Center Research Institute, reported on the cancer preventive activity of green tea among breast cancer patients. Epidemiological studies with 472 breast cancer patients revealed that increased consumption of green tea was closely associated with decreased numbers of axillary lymph node metastases among premenopausal breast cancer patients in stage I and II, and with increased expression of progesterone receptor and estrogen receptor among postmenopausal ones, resulting in improvement of prognosis with decreased recurrence.

Dr. Masami Suganuma, Saitama Cancer Center Research Institute, revealed a new function of tumor necrosis factor-α (TNF-α) as an endogenous tumor promoter and a central mediator of chronic inflammatory diseases (although TNF-α was originally identified as an anticancer factor). It is increasingly clear that understanding the role of TNF-α in tumor promotion is essential in determining a new strategy of cancer prevention. Dr. Suganuma demonstrated that tumor promotion in TNF-α-deficient mice is refractory to the tumor promoters
okadaic acid and 12-0-tetradecanoylphorbol-13-acetate (TPA), suggesting that TNF-α is the key cytokine in tumor promotion. She also presented various results showing that other inflammatory cytokines, such as interleukin (IL)-1 and IL-6, play a part in tumor promotion.

Dr. Naoko Sueoka, Saga Medical School, revealed a new preventive effect of green tea on life-style related diseases. This idea was the result of long-running experiments in tumor promotion which proved that TNF-α, an endogenous tumor promoter, is a central mediator in chronic inflammatory diseases (see the paragraph on Dr. Suganuma’s remarks). Since green tea inhibits TNF-α expression in the cells and TNF-α release from the cells, it was thought that green tea might be a preventive agent for chronic inflammatory diseases. Experiments showed that drinking green tea inhibited expression of TNF-α and IL-6 in the lungs of TNF-α transgenic mice, and the results of a prospective cohort study in Saitama Prefecture, Japan, clearly demonstrated a decreased relative risk of death from cardiovascular disease and life-prolonging effects on cumulative survival among those drinking at least 10 cups per day.

Dr. Porntipa Picha, Research Division, National Cancer Institute, Bangkok, reported on utilization of Thai herbs in cancer prevention, treatment and palliative care. Using the cytotoxic activity of various cell lines, Dr. Porntipa found that curcusone A, curcusone C and curculathyrame B—all isolated from the roots of Jatropha curcas, a local tea (processed and non-processed)—along with extract of Ganoderma lucidum and royal jelly were possible anticancer agents. A well-known Thai folk remedy for cancer patients consists of ingredients from five species of plants and five species of animals, and, in collaboration with the National Cancer Institute in the United States, the cytotoxic activities of this remedy are now under investigation.

Dr. Hideki Arimochi, Department of Biochemistry, Tokushima University, reported the results of a collaboration with Thai scientists: a study with gut microflora found that a culture of Lactobacillus acidophilus and Clostridium perfringens inhibited the number of aberrant crypt foci (ACF) in rats; a cell suspension of a new Escherichia coli strain carrying a plasmid with lactococcus biosynthetic genes led to a decrease in ACF formation, and a new Bacteroides uniformis strain carrying a plasmid with human lactoferin gene showed similar inhibitory effects; and intestinal bacteria that were genetically modified to produce chemopreventive agents inhibited colon carcinogenesis in animal experiments.

Cancer therapy

This session included four presentations. Dr. Sumitra Thongpraserth, Division of Medical Oncology, Chiang Mai University reported on the present status and treatment of lung cancer in Thailand, where lung cancer ranked among the first ten leading sites of cancer for both sexes in 1997. Unfortunately, most lung cancer patients are in the inoperable stage III or the metastatic stage IV, and in the hospital they are usually treated with paclitaxel and carboplatin. Based on reports that megestrol acetate stimulates appetite and body weight gain in cancer patients with cachexia, Dr. Sumitra administered it to 40 patients, along with paclitaxel and carboplatin. The addition of megestrol acetate to chemotherapy resulted in an increase of body weight and serum albumin, but the results were statistically not significant, although partial remission was found in 30.7% of patients. Thus, an early detection method for lung cancer is urgently needed (see Dr. E. Sueoka’s presentation).

Dr. Suresh V. Ambudkar, Division of Basic Sciences, National Cancer Institute, USA, reported on the mechanism of action of the multidrug resistance-linked ATP binding cassette (ABC) transporters, which include P-glycoprotein (Pgp), a multidrug resistance-associated protein and a mitoxantrone-resistance protein, all of which function as ATP-dependent efflux pumps. In his presentation, the drug-binding sites and ATP binding site of Pgp, along with the kinetics of ATP hydrolysis, were analyzed.

Dr. B. Rohova, Academy of Sciences of the Czech Republic, reported three results, as follows: 1. Polymer-bound drugs (mitomycin C and doxorubicin)—non-targeted or targeted with monoclonal antibodies—do not induce expression of FasL on selected cancer cells, thus protecting effector cells of the immune system against Fas-counterattack; 2. Pre-treatment with polymer-bound doxorubicin not only protects, but also mobilizes the defense mechanisms of the tumor-bearing hosts; 3. Treatment with selected monoclonal antibody-targeted polymer-bound doxorubicin causes a rapid and complete rejection of established tumors and generates prolonged systemic anti-tumor immunity.

Dr. Nisa Chawapun, Department of Radiology, Chiang Mai University, gave a comprehensive review on the role of p53 in human carcinogenesis and emphasized that p53 gene therapy can be integrated with existing therapies for better local tumor control.

Molecular mechanisms of cancer

Dr. Eisaburo Sueoka, Saga Medical School, spoke on the overexpression of heterogeneous nuclear ribonucleoprotein B1 (hnRNP B1) as a new diagnostic biomarker for human lung cancer. As Dr. Sumitra had previously indicated, early detection of lung cancer in humans is the most urgently needed step toward extending survival of patients. Dr. Sueoka reported that hnRNP B1 protein was strongly expressed in 100% of stage I lung cancer cases, and elevation of hnRNP B1 was further confirmed in both roentgenographically occult lung cancers and bronchial dysplasia. Anti-hnRNP B1 antibody was also useful for detection of
squamous cell carcinomas of oral and esophageal tissues, and even in oral leukoplakia, suggesting that hnRNP B1 will be a useful diagnostic biomarker for the early stages of lung cancer and various squamous cell carcinomas in humans.

Dr. Yasuhito Yuasa, Department of Molecular Oncology, Tokyo Medical and Dental University, identified molecular risks of gastric cancer by analyzing the methylation status of hMLH1 and expression of development-related genes. Methylation of the mismatch repair gene hMLH1 was observed in 9 of 100 gastric cancers, but it was not found in normal intestinal metaplastic tissues adjacent to cancers, indicating that this condition may be specific to gastric cancers. The expression of CDX2 gene appeared to decrease progressively with the transition from well to poorly differentiated cancer cell lines; the expression of GATA4 and GATA5 genes was undetectable in several cell lines. Dr. Yuasa concluded that these gene aberrations may be related to gastric cancer and may play a role as risk factors.

In Africa, higher aflatoxin-albumin adduct levels were observed in hepatitis B virus (HBV) infection compared with those in uninfected children. Dr. Christopher P. Wild, Epidemiology and Health Services Research, School of Medicine, University of Leeds, UK, observed that, in Gambia, the strongest determinants of aflatoxin-albumin adducts were season and place of residence rather than HBV status or interindividual variations in aflatoxin metabolizing enzymes. Furthermore, exposure to HBV and aflatoxins occurs early in life, with evidence of transplacental aflatoxin exposure in Gambian children. Reduction of aflatoxin exposure and introduction of HBV vaccination were discussed.

Dr. Kazuhiko Uchida, Institute of Basic Medical Sciences, University of Tsukuba, presented the results of joint work with Kohn Kaen University and National Cancer Institute, Bangkok. Comparative genomic hybridization with quantitative polymerase chain reaction was performed on fresh frozen tissue from over 50 gallbladder cancers and intrahepatic biliary cancers in order to identify abnormality patterns of genomic copy number and oncogenes and tumor suppressor genes involved in the development and progression of these cancers. In Thailand, most intrahepatic biliary cancers examined were liver fluke-infected cases with chronic inflammation. Recurrent chromosomal gains were more prominent in gallbladder cancer than were chromosomal losses. Dr. Uchida discussed the usefulness of genomic phenotyping for classification of cancer types.

Dr. Sunro Sonoda, Department of Virology, Kagoshima University, reported on the prevention and control of human T-cell leukemia virus (HTLV) infection. Both HTLV and human immunodeficiency virus (HIV) are members of a family of retroviridae which are causatively associated with T-cell leukemia and acquired immunodeficiency syndrome (AIDS). The host immune response to HTLV or HIV is initiated by the recognition of viral peptides for human leukocyte antigen (HLA) molecules. Thus, HLA molecules play a key role in the prevention of HTLV and HIV infections and related diseases. Dr. Sonoda found an anti-HTLV effect of green tea, which induces apoptosis in HTLV-infected T-cells. Consequently, the prevention and control of chronic HTLV infection by drinking green tea is under investigation. Furthermore, in Chiang Mai a study on the possibility of preventing AIDS by drinking green tea is now under way, a project supported by the Royal Project Foundation and the Saitama-Thailand Friendship Association.

We Japanese scientists very much thank the members of the Program Committee led by Dr. Usanee Vinitketkumnuen, Head of Department of Biochemistry, Faculty of Medicine, Chiang Mai University and Dr. Somyos Deerasamee, Director of National Cancer Institute, Bangkok for their arrangements in organizing this superb Symposium—and especially for including the Memorial Lectures for Prof. Wada. Prof. Wada also contributed to the development of cancer research in Japan by serving in numerous respected positions, such as President of the Japanese Cancer Association (1986), Chairman of the Council of the Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health and Welfare, Japan, and Chairman of the Board of Directors of the Princess Takamatsu Cancer Research Fund, to name a few. For his outstanding contributions in clinical cancer research, Prof. Wada was awarded the first Nagayo-Mataro Prize of the Japanese Cancer Association in 1997.

This Symposium provided us with new insights and perspectives, further fruits of Prof. Wada’s cosmopolitan cancer research. In this success, the collaboration between Drs. Maitree Suttajit and Kei Nakachi supported by the Ministry of Education, Science, Sports and Culture, Japan, played an important role. Finally, all participants agreed that this Symposium was useful in strengthening the firm friendship and scientific bridge between our two nations.

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