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*This English Edition is a translation of the newsletter published in Japanese on October 30, 2009
The 17th International Symposium of AHCC Research Association was held at Roiyton Sapporo Hotel (Sapporo, Japan) on July 25 and 26, 2009, under the auspices of the Hokkaido Bureau of Economy, Trade and Industry, Ministry of Economy, Trade and Industry.

The symposium started with a keynote address entitled "Nutrition and care of cancer patients" given by Professor Richard J. Andrassy, Department of Surgery, University of Texas Health Science Center. There were 33 presentations this year, including 19 and 14 reports on basic and clinical research, respectively, of which 12 were poster sessions. There were 301 participants in all, including 79 overseas participants from 11 countries.

As a recent trend, many researchers have reported studies with a focus on alleviation of adverse drug reactions of anticancer agents with concomitant use of AHCC. Assistant Prof. Hiroaki Yanagimoto (Department of Surgery, Kansai Medical University), Associate Prof. Judith Smith (The University of Texas, MD Anderson Cancer Center), and others gave presentations on the above theme. Dr. Yoshihito Sumiyoshi (Urology, Shikoku Cancer Center, currently Urology, Koto Hospital, Japan) presented the results of a clinical study of AHCC entitled "Usefulness of AHCC for Prostate Cancer Patients Undergoing Active Surveillance". This MHLW cancer grant study was conducted in 7 medical institutions across Japan, in which, while decease of the serum PSA by over 50% was achieved in only 1 patient, the compliance with AHCC treatment was excellent in general, and no adverse drug reactions were observed. QOL evaluation revealed a significant decrease in anxious feeling, demonstrating some favorable results.

In addition, there were 15 presentations on Oligonol. Prof. Mikio Nishizawa, et al. (College of Life Science, Ritsumeikan University, Japan) presented the results of a double-blind, placebo-controlled study, in which a relatively low dose (100mg/day) of Oligonol was administered to collegiate distance runners during a long-term training camp. The results showed decreases in the inflammatory fatigue markers in the blood, suggesting an anti-fatigue effect of Oligonol mediated by its anti-inflammatory effect. Furthermore, Adjunct Prof. Miku Kusakabe (Tokai University, Japan) gave a presentation entitled "Effect of Oligonol Supplementation on Oxidative Stress and Antioxidant Capacity following High-Intensity Intermittent Sprint Cycle Exercise". Their presentations gave the clear impression that study results have accumulated in the area of the anti-fatigue effects of Oligonol and improvement of exercise performance by AHCC.

In the post-conference party on the opening day, the first winners of the AHCC fellowship, established this year, were announced. Assistant Prof. Hiroaki Yanagimoto received the Excellent Study Report Award from the Director-General, Hokkaido Bureau of Economy, Trade and Industry, Ministry of Economy, Trade and Industry. Assistant Researcher Miki Sakae (Osaka University Graduate School of Medicine, Japan) received the Excellent Poster Session Award from the chairman of the AHCC Research Association, and Associate Prof. Judith Smith (The University of Texas, MD Anderson Cancer Center) received the Young Researcher Incentive Award. This fellowship has been established to encourage young researchers engaged in the area of complementary and alternative medicine to study functional foods such as AHCC and others.

This system is expected to serve as an incentive for young researchers.
Developers and marketers of clinically proven nutraceuticals in the U.S. face similar challenges to those faced by their counterparts all across the globe. They have to communicate how their product can help therapy-seeking patients and prevention-minded consumers under highly restrictive regulatory conditions that are applied blindly to all products, irrespective of their underlying research. So while a company may have a nutraceutical product that can help tens or even hundreds of thousands of people based on compelling clinical research, it is simply impossible for them to get the word out to those people that the product exists and that it works.

This unfortunate dilemma is the product of a poor regulatory structure which provides Americans with access to pharmaceutical compounds but which severely restricts their ability to benefit from highly effective natural compounds simply because they are naturally and not synthetically derived. Or to put it another words, our regulatory system effectively tells us to choose a synthetic compound over a naturally derived product irrespective of their comparative efficacy and safety.

This is a fact that most members of the mainstream U.S. medical community fail to consider. Their usual position is that “if the FDA hasn’t approved it as a ‘novel drug’, then my patient shouldn’t be on it.” However, interestingly, once medical doctors hear the case for why even a highly efficacious clinically proven naturally-derived product cannot reach patients who could benefit from it, they tend to become significantly more open-minded. Therefore, it is imperative for nutraceutical companies to make this case to the doctors as a means of getting them to consider natural compounds in therapy, to accept supporting clinical trials that are convincing but not as large as those that pharmaceutical companies can afford to do, and ultimately to recommend nutraceutical products to their patients.

One of the primary reasons why medical doctors are highly skeptical about dietary supplements and advise their patients against using them is directly related to the lack of guidance by the FDA. The Agency does not provide any such guidance on efficacy of supplements and its safety validation is limited to a small number of compounds that had applied for and received “New Dietary Ingredient” status (ingredients that were used prior to 1994 do not require any safety validation from the FDA). Since the FDA’s only benchmark for efficacy is the “Novel Drug Status” approval, many doctors simply conclude that effective nutraceuticals should just be registered as “novel drugs”. Their failure to understand the true barrier to getting a natural compound obtain such approval is one of the key reasons for their reluctance to consider nutraceuticals for use in their practice.

The “Novel Drug” approval process is at the very heart of the U.S. pharmaceuticals industry and can be thought of as a the cycle that feeds itself. The approval requires very large clinical trials that are
extremely costly. Such large trials can be funded by pharmaceutical companies or venture capitalists backing biotechnology start-up companies only if they can collect high prices for those drugs once they are on the market. High prices, in turn, can only be maintained if health insurance companies agree to cover those drugs, which means that the intellectual property behind the drugs must be “bullet-proof” so that no other company can make a similar product.

Therefore, if a biotechnology investor or pharmaceutical company does not have full confidence that their compound cannot be emulated, they will not provide the money to fund the very large trials needed to get the novel drug approval status even if they believe that the likelihood of a successful trial is reasonable. So what many doctors fail to realize is that efficacy is not the only requirement for the “novel drug” approval status – the strength of the intellectual property is an equally important factor.

And this is the heart of the problem – it is much more difficult to gain confidence in the strength of a patent behind a natural compound (which is a complex molecule with multiple bioactive components which may work synergistically) than behind a single molecule synthetic compound. This is why when pharmaceutical companies come across natural compounds that promise efficacy, they immediately start trying to figure out if they can make synthetic version of the same. For example, in 1998, Pfizer bought global licensing rights to “hoodia cactus” extract (containing an appetite-suppressing compound called P57) so that it can develop a synthetic version of the same while keeping the natural extract off the market. When it failed to produce a synthetic version of P57, Pfizer exited the project – pursuing a “novel drug” approval on the natural form of the extract was not viable from their standpoint.

This is the predicament that applies to most natural products and it is the reason why there are so few natural products that are sold as drugs. One of the few exceptions is high concentration fish oil (now sold under the brand name “LOVAZA”), which managed to get FDA approval and protect its patents. But ironically, while having succeeded in the U.S., this same patent was invalidated in Europe further emphasizing the risks that investors face in backing the “novel drug” registration of natural products.

The IP issue makes the entire ”Cycle” unwind. Without full confidence in IP of natural compounds, investors fall away. So there is no funding for large trials, which means there is “no novel drug” approval. Without the drug approval, there is “no insurance coverage”. And without that, the product price have to be low which means that there are not enough returns to investors to fund large trials. Instead you can only do smaller trials with dozens of patients rather than with thousands. What is even worse is that without the “novel drug” approval and in the absence of any other lower health claim approval standard, you are very restricted in regard to the product claims you can make irrespective of the supporting research. So this further hurts your ability to sell, which means that you even have less capital available for

Many supplements are sold in the U.S. Quite a few manufacturers have invested clinical studies of supplements.
large trials.

What all of this effectively means is that you can have a compound that is not registered as a “novel drug” for only one reason: that it happens to be natural. So when a medical doctor says “if this ingredient is so good, why isn’t it registered as a drug?”, the answer can be “simply because it is natural.” Hopefully, the explanation of the novel drug approval “Cycle” described above can convince the doctor that the fact that a nutraceutical is not registered as a “novel drug” does not say anything about its efficacy.

The “Cycle” also helps address the second major set of objections that doctors typically voice about nutraceuticals – that their trials are too small. The explanation presented should show the doctors why economically, it is impossible to conduct large trials on any compounds that don’t have the novel drug status. This, in turn, would hopefully stop the doctors from dismissing nutraceutical products simply because they don’t have pharmaceutical drug size trials.

The explanation of why nutraceuticals are not registered as novel drugs is important but it is not sufficient in convincing medical doctors to use a nutraceutical product. Just as importantly, you have to make the case that the natural compound that you are presenting has the clinical trials that put it on par with registered novel drug compounds (albeit on the basis of smaller size trials). And unfortunately there are very few ingredients in the nutraceutical industry that would meet this criteria.

AHCC is one of the compounds that is definitely in this group. It is extremely rare to see a nutraceutical compound supported by more than 25 PubMed-listed peer reviewed studies and backed by a 9-year 269-patient study published in a highly prestigious journal that shows significant efficacy of the compound! All of the medical doctors who take the time to review the research on AHCC are extremely impressed with this clinical trial lead by Dr. Kamiyama. The fact that the 44-patient study lead by Dr. Cowawintaweewat in Thailand showed consistent results further helps to reinforce the efficacy of AHCC. The clinical study at Yale Medical School that showed improved cytokine response in health elderly patients and the double-blind placebo-controlled study published in the journal “Nutrition and Cancer” showing improved dendritic cell activity clearly demonstrate the compound’s mode of action, which medical doctors are also very interested in seeing.

There is a handful of nutritional supplements that are widely recommended by a significant number of mainstream doctors. This include folic acid recommended by obstetricians, calcium and vitamin D endorsed by Orthopedists, CoQ10 and fish oil embraced by many cardiologists and select probiotics that are increasingly recommended gastroenterologists. The vision and mission for AHCC is that it becomes equally broadly endorsed by oncologists and hepatologists throughout the U.S. The growing adoption of AHCC particularly by cancer and liver disease patients, the large body of clinical research on AHCC that increases significantly each year and the significant efforts to educate U.S. medical doctors is helping pave the way for such broad adoption of AHCC by medical doctors in the United States.
The luncheon seminar of The Japanese Society of Nutrition and Dietetics was a great success, demonstrating the high level of interest on metabolic syndrome.

The European Society for Clinical Nutrition and Metabolism (ESPEN)

The 31st Conference of The European Society for Clinical Nutrition and Metabolism was held in Vienna (Austria) from August 29 to September 1, 2009.

ESPEN focuses on nutrition, with many members gathered not only from European countries, but also from the U.S. and Japan. In recent years, the results of studies on AHCC and Oligonol have been presented at ESPEN conferences. This time, speakers from The University of Granada (Spain), Kansai Medical University, and Ritsumeikan University reported on their studies of AHCC and Oligonol. Ph.D. Olga Martínez–Augustin (The University of Granada) reported on the effects of AHCC on the intestinal cellular responses and differentiation. Assistant Prof. Hiroaki Yanagimoto’s group (Kansai Medical University) administered AHCC to patients with pancreatic/biliary tract cancer concurrently with chemotherapy and reported a reduction in the incidence of chemotherapy-associated adverse drug reactions and improvement of the QOL of the patients. Prof. Mikio Nishizawa (College of Life Science, Ritsumeikan University) reported inhibition of NO production in hepatocytes as a result of the anti-inflammatory effects of Oligonol.

This conference, with a focus on "clinical nutrition", included not only presentations of the study results of various functional materials, but also discussions about the feasibility of application of polysaccharides as well as δ-3 and amino acids (arginine, glutamine, etc.) that have been attracting attention.

As it is believed that AHCC contains polysaccharides such as α-glucan as its main ingredients, these presentations focusing on “intestinal environment and immunology” drew a lot of attention from clinicians.

The 56th Annual Meeting of The Japanese Society of Nutrition and Dietetics - Luncheon Seminar

This luncheon seminar, sponsored by Amino Up Chemical Co., Ltd., was held at the Sapporo Convention Center on September 3, 2009. Associate Prof. Kazuisha Maeda (Department of Complementary and Alternative Medicine, Osaka University Graduate School of Medicine, Japan) gave a presentation entitled "Good Diet for Prevention of Metabolic Syndrome". Prof. Yasuhisa Shinomura (1st Department of Internal Medical, Sapporo Medical University), who also graduated from Osaka University like Prof. Maeda, served as the chairman of the seminar. Numbered tickets for 180 seats for the luncheon seminar were sold in no time, and many people lingered on to get a chance to listen to the lecture, and almost 240 seats were filled up.

Prof. Maeda, famous for his discovery of adiponectin, proposed intake of healthy lipids such as δ-3 fatty acids and unrefined carbohydrates to prevent metabolic syndrome. He gave his lecture using some data on the prophylactic effects of this diet against the onset of metabolic syndrome and other diseases, and mentioned the practical use of Oligonol and other functional foods towards the end of his lecture. The seminar room was filled with many listeners, keenly taking notes during the lecture, showing the high level of interest in this research theme.

Participants ardently listening to poster presentations on an AHCC-related theme at ESPEN

Executive Meeting (9·14)

The Executive Meeting is held by a policy research group to discuss various topics from an ideal labeling system to enactment of laws for health foods. It was called for by concerned manufacturing workers and started in 2007, against tightening of regulations such as “413 Office memo” issued by the MHLW in 2007 to abolish brand names that might conflict with Pharmaceutical Affairs Act, and many meetings have been held since then.

At the Executive Meeting held on September 14, there was a panel discussion entitled "Efforts for introduction of a functional labeling system in local governments". There were presentations by Mr. Taku Kajiwara (The former president of the National Governors’ Association, Representative of Kenko Iryo Shinmin Kaigi (Healthcare Municipal Civic Conference), Mr. Masaki Kawai (Section of New Industry Planning, Department of Industry, Labor, and Sight-seeing, Niigata Prefectural Government), and Dr. Takehito Miura (Lead Manager of Planning & Steering Committee, Hokkaido Association for Bio-Business), and all of these speakers presented their efforts to promote food labeling bearing claims of the functions in their communities. Mr. Kawai introduced their activities appealing for transfer of authority for approval of specified health foods in Niigata prefecture. Dr. Miura explained suggestions from Hokkaido as a special regional system district. Among the suggestions, there was a request to admit labeling bearing usefulness claims at stores for primary products and processed products from Hokkaido, which has been approved by Hokkaido Prefectural Assembly. Mr. Kajiwara emphasized the importance of patient organizations, civilian groups and citizens participating in politics, in anticipation of transition from bureaucratic politics to civil politics, in the midst of the recent political power shift.

The current legal system does not allow food labeling bearing function/indication statements, and even if a newly developed functional food has attractive features, they cannot be conveyed to consumers by any legal means. It would appear necessary for local government and manufactures to cooperate, point out the precise problems with the current legal system to the Japanese government, and suggest establishment of an alternative system.
The Latest Publications and Academic Presentations

*Presenting the titles of research that have appeared in international journals and academic conferences so far this year.

Publications

**Medical Science Digest, 35 (6) : 241–244** (2009)
“Potentiating of AHCC on Natural Immunity”
Hiroshi Nishiboka, Yuusuke Akao, et al.
(Amino Up Chemical Co., Ltd., Hokkaido University Graduate School of Medicine)

**Natural Medicine Journal, 1 (1) : Online Documentation (2009)**
“Improved Survival of Patients with Gastric Cancer or Colon Cancer when Treated with Active Hexasome Correlated Compound (AHCC) : Effect of AHCC on Digestive System Cancer”
Yuusai Kawaguchi
(Kansai Medical University)

**3rd International Symposium on Nutrition, Oxygen Biology & Medicine (Paris, France)**
“New Lychee Fruit-Derived Polyphenol Oligonol Converted into a Low–Molecular Form Improves Exercise-Induced Fatigue”
Hideki Ono, et al.
(Kyorin University Graduate School of Medicine, Japan)

**The 62nd Annual Meeting of the Society for Free Radical Research Japan**
(Fukuoka, Japan)
Jun. 11 (Thu.)–12 (Fri.), 2009
“Suppressive Effect of Depolymerized Polyphenol Product "Oligonol" for Reactive Oxygen in Humans”
Kazumasa Aoyagi
(Center for Integrative Medicine, Tsukuba University of Technology)

**The 15th International Symposium on Atherosclerosis (Boston, USA)**
Jun. 14 (Sun.)–18 (Thu.), 2009
“Effects of Lychee Polyphenol on Postprandial Hyperlipidemia”
Kazuo Kondo, et al.
(Institute of Environmental Science for Human Life, Ochanomizu University)

**Chemoprevention and Translation Research**
(Langkawi, Malaysia)
Jul. 9 (Thu.)–12 (Sun.), 2009
“Oligonol, a Low Molecular Weight Polyphenol Formulation, Inhibits UVB-Induced Lipid Peroxidation and COX-2 Expression, and Induces NQO1 in Hairless Mouse Skin”
Joydeb Kumar Kundu, Young-Joon Surh, et al.
(Seoul National University)

**FOOD FUNCTION, 5 (1) : 2–7 (2009)**
“Anti–Oxidative Effects of Oligonol, New Oligomerized Polyphenol Formulation”
Hideki Ono, Takuya Sakurai, et al.
(Kyorin University Graduate School of Medicine, Japan)

“Preventive Effects of Oligomerized Polyphenol on Estradiol-Induced Prostatitis in Rats”
Dong Suk Kim, Sung Joon Hong et al.
(Yonsei University College of Medicine)

**The 10th International Congress of Integrative Medicine (Tokyo, Japan)**
Jul. 18 (Sat.), 2009
“Therapeutic Gaps between the Evidence-Based Medicine (EBM) and Cancer Patients in the Advanced Stage or Recurrence : Review of Cancer Therapy with AHCC and GCP under Individual EBM from a Long-Term Follow-up over 11 Years for Cancer of the Lung and Breast”
Reiki Ishizuka
(Tajima Clinic)

**31th ESPEN Congress 2009 (Vienna, Austria)**
Aug. 29 (Sat.)–Sep. 1 (Tue.), 2009
“The Beneficial Effect of Active Hexasome Correlated Compound (AHCC), a Health Food Component, in Patients with Pancreatic or Biliary Tract Cancer who underwent Chemotherapy”
Hiroaki Yanagimoto, et al.
(Department of Surgery, Kansai Medical University)

**The 56th Annual Meeting of The Japanese Society of Nutrition and Dietetics : Luncheon Seminar (Sapporo, Japan)**
Sep. 2 (Wed.)–4 (Fri.), 2009
“Good Diet for Prevention of Metabolic Syndrome”
Kazuhisa Maeda
(Okayama University Graduate School of Medicine, Japan)

Academic Presentations

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Editorial Postscript

The symposium closed before the start of the summer season this year. However, Hokkaido never really experienced any real summer in 2009, becoming cold rather rapidly, and we can now feel the autumn coming. Harvesting conditions are not good due to the low temperatures and insufficient sunlight during the summer, although beer gardens along Odori Park seemed to still attract many people. These beer gardens closed before the Obon holidays in August, and in recent years, people in Hokkaido have had to endure few warm days that allowed them to visit the beer gardens. For citizens to enjoy the short summer in Hokkaido, I really want the local government to be more flexible about extension of the beer garden season. We had a few, brief summer days during the Obon period, and Hokkaido is now plunging into snowy winter. We may hear news reports of the first snowfall here in Sapporo when this journal is delivered to you.

(Takehito Miura)