

Meeting Report: 4th Biennial meeting of the Society for Free Radical Research - Asia, held during July 9-12, 2009 at Langkawi, Malaysia

The 4 Biennial meeting of the Society for Free Radical Research - Asia was co-organized with 7th COSTAM/SFRR (Asia/Malaysia) International Workshop 2009. The meeting was organized by SFRR-Asia/Malaysia, the Malaysian Palm Oil Board, the Confederation of Scientific and Technical Associations in Malaysia (COSTAM) and University Kebangsaan Malaysia. The organizers were: Tan Sri Datuk Dr Augustine S H Ong, Datuk Dr. Mohinder Singh, and Dr. Kalanithi Nesaretnam. The meeting was supported by many sponsors, including the Oxygen Club of California and commercial companies. More than 250 participants from over 15 countries participated. The scientific deliberations included a keynote address, over 60 invited lectures, 6 oral presentations for young investigator awards and more than 110 posters which were available for reading and discussion during the breaks and a specific poster session. Business meetings of SFRR-Asia and the 'Free Radical Research' editorial board were also held during the meeting.

Inauguration and keynote address on July 9, 2009

The meeting was inaugurated by His Royal Highness, the Crown Prince of Perak Darul Ridzuan. The chairman of the organizing committee and President-Elect of SFRR-Asia, Dr. Kalanithi Nesaretnam delivered her welcome address. Then there was a short cultural program. This was followed by a keynote lecture on 'Mitochondrial regulation of cell death' by Prof. Sten Orrenius from the Karolinska Institute, Sweden. Mitochondrial malfunction has been implicated in the pathogenesis of a variety of disorders, including neurodegeneration and cancer. Stabilization of the mitochondria by antioxidants, or other compounds supporting the activity of respiratory chain, can protect them, and also display beneficial effects when administered to patients with neurodegenerative diseases. In contrast, stabilization of the mitochondria in cancer cells contributes to their resistance

to treatment. The stimulation of destructive processes in tumor mitochondria could be a useful approach to promote mitochondrial collapse and cell death processes. This successful start to the meeting was followed by a welcome reception at the beach.

The scientific sessions held over the following three days were focused on:

- Session I. Tocotrienols and tocopherols
- Session II. Polyphenols
- Session III. General
- Session IV. Oxidant signaling
- Session V. Clinical research & SFRR-Asia Young Investigator award oral presentations

July 10, 2009

Session I. Tocotrienols and tocopherols

This session was chaired by Datuk Dr. Mohd Basri Wahid from Malaysia and Dr. Maret Traber from USA.

The vitamin E group of compounds, comprising of tocotrienols and tocopherols occupy a prime position among beneficial lipid soluble antioxidants. Tocotrienols, present in palm oil, rice bran oil and other plant foods present in the Asian region are attracting a lot of attention in recent years due to their potential health benefits. The first special presentation was by Prof. Bharat Aggarwal (MD Anderson Cancer Research Center, USA). He presented his interesting and in-depth talk on 'Targeting inflammatory pathways by tocotrienols for prevention of chronic diseases'. He described the link between inflammation, cancer and NFκB. The current trend seems to be moving from 'single drug magic bullets to polypharmacology'. Tocotrienols are similar to statins in their action. Nutraceuticals may prove to be better than pharmaceuticals. Prof. Maret Traber (Linus Pauling Institute, USA) then gave a talk on 'Vitamin E update' She mentioned about vitamin E action in target groups and interaction between vitamins E and

C. Prof Lindsay Brown (Australia) gave a talk on 'Cardiovascular symptoms in diet-induced diabetes in rats can be prevented or reversed by tocotrienols'. He talked about tocotrienols and alpha-lipoic acid in fructose induced diabetes model and resulting cardiovascular events. A number of parameters were analyzed. Dr. G.P. Tou (Malaysia) delivered a lecture on 'The vitamin E paradox. This was followed by a lecture on 'Effects of tocotrienols on the hypercholesterolemic rabbit hearts' by Prof. Dipak Das (USA). Prof. D.Y.Y. Leng (Singapore) described how 'gamma-tocotrienol suppresses prostate cancer cell proliferation and invasion through multiple signaling pathways. The last lecture of this part of the session was by Dr. Sree Kumar (USA) on the development of gamma-tocotrienol as radiation counter measure drug.

The second part of the session, contained 5 lectures. The first lecture by Dr. Wan Ngah (Malaysia) discussed how tocotrienols reduce DNA damage and affects protein expression in human lymphocytes from two different age groups. Dr. Kartal-Ozer (Turkey) then described how hypercholesterolemia can induce oxidative stress in brain of rabbits. The next lecture by Dr. Michael Mathai (Australia) showed how oral supplementation with tocotrienols reverses hypertension and cardiac fibrosis in obese-hypertensive model of rats. Then Dr. Kalanithi Nesaretnam from Malaysian Palm Oil Board described her significant findings from clinical trials in relation to breast cancer incidence and tocotrienols consumption/levels. The last lecture in this session was by Dr. Ammu Radhakrishnan (Malaysia) on the enhancement of immune response by tocotrienols in relation to breast cancer.

This session was followed by the SFRR-Asia business meeting. Representatives from many countries of the region participated (e.g. Japan, Korea, China, Thailand, Taiwan, Malaysia and India) and included the current President Dr. T.P.A. Devasagayam, Past-President Prof. B. Zhao, President-Elect, Dr. K. Nesar-etnam, Secretary-General Dr. Naito, and Treasurer Dr. Majima. The major activities of SFRR-Asia were discussed and next committee members and venues for meetings were finalized. Prof. Naito and Prof. Majima will continue to be Secretary-General and Treasurer of SFRR-Asia respectively for two more years and the next SFRR-Asia President-Elect is to be chosen by Korean SFRR. Dr. Majima also gave a presentation about the Free Radical School being held in Japan.

The post-lunch session contained three lectures. The first was given by Dr. Y.K. Hay (Malaysia) on absorption and distribution issues in the research and utilization of the tocotrienols. The second one by Dr. P.G. Bagali (India and Malaysia, with work

carried out in both countries) pertained to computer modeling approaches in the development of tocotrienol-based compounds. The final lecture was given by Dr. Sharon Campbell (USA) on tocopherols and tocotrienols in relation to prostate cancer, a major form of this disease in the USA.

Session II Polyphenols

This session was chaired by Prof. Cesar Fraga (USA/Argentina) and Dr. Yasmin Yusof (Malaysia), with the opening presentation given by Prof. Helmut Sies (Germany), Past-President of SFRR-International. He gave a comprehensive view of new developments in flavonoid research in relation to vascular diseases. The next talk was by Prof. Cesar Fraga (USA) who described the antihypertensive effects of flavonols. The final presentation was by Prof. Alan Crozier (UK) on the bioavailability of dietary flavonoids and phenolics.

This was followed by the Poster session in which a large number of interesting posters were presented by students and young researchers from different countries. These posters were evaluated by a panel of judges for SFRR-Malaysia awards and 'Free Radical Research' Poster awards.

The subsequent session contained three presentations. The first by Dr. David Ross (USA) was on the discovery and development of targeted antitumour quinines. Prof. Baolu Zhao, Past President of SFRR-Asia (China) then gave a lecture on protective effect of green tea polyphenols against 6-hydroxydopamine-induced apoptosis through ROS-NO pathway in Parkinson's disease models. The last presentation of the day was by Dr. Rajesh Agarwal (USA) on the skin cancer chemoprevention by silibinin.

July 11, 2009

Session II was chaired by Prof. Helmut Sies (Germany) and Dr. Wan Zurina Wan Ngah (Malaysia)

The first lecture in this session was by Dr. Daniel Tsun-Yee Chiu (Taiwan). His talk showed that myocardial infarction and Parkinson's disease are associated with increased oxidative stress and that means to suppress oxidative damage or to enforce anti-oxidative functions should be beneficial to certain patients with acute myocardial infarction or Parkinson's disease. The next lecture was by Dr. Choon-Nam Ong (Singapore) on carotenoids and risk of acute myocardial infarction, the study being carried out among the Chinese in Singapore. This study supports a cardioprotective role for xanthophyll carotenoids in humans. Dr. Patricia Oteiza (USA/Brazil) then presented her recent data on edox signaling in leukemia

and lymphoma cells: regulation by polyphenols and other selective inhibitors. These studies suggest that several signaling pathways should be targeted when designing therapeutics for Hodgkin's lymphoma. The next lecture was by Dr. Devasagayam (India) on the radiomodulating and antioxidant effects of baicalein, a polyphenol present in medicinal plants. His study revealed that baicalein acts as a radioprotector in normal tissues and cells, but shows radiosensitizing effect in tumour cells. Hence, this has got potential for use in radiotherapy of cancers. The next lecture was given by Dr. Uma Devi Palanisamy (Malaysia) on phenolic compounds as antihyperglycemic agents. Her study involved screening of 15 Malaysian plant extracts for possible components for antioxidant and antihypoglycemic activity. Dr. Maitree Suttajit (Thailand) then talked about antioxidant and chemopreventive potential of polyphenolic compounds from some Thai fruits with special emphasis on the fruit 'Mao Lugang' (*Antidesma thwaitesianum* Muell.Arg.). Finally, Dr. Guy Haegeman (Belgium) presented his data on the modulation of inflammatory gene expression by natural compounds. The compounds examined include withaferin A from *Withania* species, soy isoflavones and a stabilized compound (CpdA) derived from salt brush in the Kalahari deserts of Africa.

The following session had 5 speakers. The first was Dr. Asmah Rahmat (Malaysia) who gave a comparison of total phenolic content and antioxidant activity of some fresh herbs/spices (turmeric leaf, pandan leaf, torch ginger) and their powder forms. This study showed that the powder forms have higher total phenolic content and antioxidant activity than the fresh forms. The next lecture by Dr. S.K. Bandyopadhyay (India) showed that an analog of resveratrol (3,5'-hydroxylated congener of trans-resveratrol) is a better anticancer agent than the parent compound and overcomes the contra indicative effects of non steroidal anti-inflammatory drug-induced gastric ulcer. The following lecture by Dr. Suhaila Mohamed (Malaysia) showed that oil palm leaf polyphenols protect against metabolic syndrome and neurodegeneration in rats. Dr. M.S. Kanthimathi (Malaysia) then showed that two woody herbaceous plants found in local forests (*Cyrtandra cupulata*, *Apama tomentosa*) have potent antioxidant and anticancer activities. Finally, Dr. U.R. Kuppasamy (Malaysia) reported that naringenin, a prominent flavonoid found in citrus fruits and tomato, may play an important role as an adjuvant and/or alternative to insulin therapy for the management of diabetes mellitus.

This session was followed by lunch and the editorial board meeting of 'Free Radical Research'. Discussions regarding possible inclusion of more members for the editorial board and how to improve circulation and impact factor were held.

Session III General

This session, running parallel to the session on Polyphenols, was chaired by Prof. E. Cadenas (USA) and Dr. Gee Ping Tou (Malaysia). The first lecture was given by Prof. Cadenas on metabolic targets in a model of Alzheimer's disease: effects of α -lipoic acid. His studies showed that lipoic acid feeding enhances Akt activity, whilst substantially downregulating GSK-3 β (glycogen synthase kinase-3 beta) activity in vivo in the brain of mice. The second lecture by Dr. Olaf Sommerburg (Germany) on carotenoid supplementation in cystic fibrosis, showed that dietary red palm oil can normalize depleted β -carotene levels of cystic fibrosis patients over a longer time span without the risk of overdosing as seen with high concentrated pharmacological supplements. This was followed by a talk by Dr. Marc Diederich on marine compounds (from the Fijian sponge *Rhabdastrella globostellata*, from the crinoid *Comanthus parvicirrus*, from the soft corals *Lobophytum* sp. and *Simularia* sp., and from the gorgonian *Subergorgia* sp.) as promising anti-cancer agents. The chemistry and the molecular mechanism of action of these compounds responsible for their NF- κ B inhibitory activity was discussed. The subsequent talk was by Dr. Hideyuki Majima (Japan) on 3D cultures of rat gastric mucosal cell line RGM1 or its tumor cell line RGK1 combined with human fibro-blasts. Dr. Sek Cheuen Chow (Malaysia) then presented data on the immunomodulation and toxicity of methylketone peptides. Dr. Aishah Adam (Malaysia) presented data on folk medicines with promising antioxidant capacities. The study showed that crude extracts of *Octomeles sumatrana* and *Syzygium poly-anthum* had high antioxidant activities as well as efficacy in vivo against oxidative-stress related conditions. The final lecture by Tasduq Abdulla (India) discussed herbal antioxidants and their role in liver pathology. The antioxidants studied were silymarin used for antifibrotic treatment, *Phyllanthus amarus* for chronic hepatitis B and glycyrrhizin to treat chronic viral hepatitis. The main mechanism of protection against liver disorders seem to involve inhibition of lipid peroxidation followed by improved intracellular calcium homeostasis and inhibition of Ca²⁺ dependent proteases and CYP2E1 (cytochrome P450 2E1).

The first lecture in the next session was delivered by Dr. Joydeb Kumar Kundu (Korea) on the possible mechanisms behind anticancer effect of diallyl trisulfide present in garlic. His studies showed that the inhibitory effects of this compound on 12-O-tetradecanoyl-phorbol-13-acetate (TPA)-induced AP-1 (activator protein-1) activation and COX-2 (cyclooxygenase-2) expression through modulation of JNK (c-jun N-terminal kinase) or Akt signaling may partly account for its anti-tumor promoting effect on mouse skin

carcinogenesis. Dr. Poonam Kakkar (India) then presented data on the modulation of Bcl-2 and Bax expression by *Fumaria parviflora* Lam. extract during nimesulide induced apoptosis in primary rat hepatocytes. The study indicated that *Fumaria parviflora* Lam. emerges as a potential hepatoprotectant with evidence for its anti-apoptotic and antioxidant properties *in vitro*. The final lecture was by Dr. Zeki Topeu (Turkey) on DNA telomerases as targets of anti-cancer drugs and alternative telomere lengthening pathways.

Session IV Oxidant signaling

This first lecture in this session, chaired by Prof. Young-Joon Surh (Korea) and Dr. Salmaan Husain (Malaysia) was given by Prof. Surh on the role of Nrf-2-mediated heme oxygenase-1 induction in adaptive cellular response to oxidative and inflammatory stresses. His study showed that CO produced by heme oxygenase-1 rescues PC12 (pheochromocytoma) cells from nitrosative stress through induction of GCLC (glutamate cysteine ligase) which is mediated by activation of PI3K/Akt and subsequently Nrf2-(nuclear factor E2-related factor-2) signaling. The next lecture was given by Prof. Michael Davies (Australia, Secretary-General of SFRR-International), on myeloperoxidase-derived oxidants: a major source of damage in human inflammatory diseases?. His studies show that two classes of compounds, namely nitroxide radicals and some phenols can be effective myeloperoxidase inhibitors, and are possible therapeutic agents for the inhibition of myeloperoxidase-mediated damage at sites of inflammation. This was followed by lecture by Prof. Yuji Naito (Japan, Secretary-General of SFRR-Asia) on the role of peroxiredoxin-6 (Prx-6) in intestinal inflammation. His studies have provided evidence for a reduction of Prx-6 and diminished antioxidant defenses in human and murine colitis. The next lecture was by Prof. Roderick Dashwood (USA) on NADPH oxidase 1 (Nox1) and related NOX isoforms as key mediators of NFκB (Nuclear factor kappa-B) signaling in colon cancer. His studies concluded that Nox-1-NFκB pathway is important in colon carcinogenesis, and that Nox1 may provide a target for novel therapeutic strategies against colon cancer development. The final lecture by Prof. Toyokuni (Japan) showed that asbestos-induced carcinogenesis is oxidative stress dependent. His studies revealed that most of the tumors examined showed homozygous deletion of CDKN2A (p16^{INK4A}). Together with analyses of asbestos-interacting proteins, modulation of iron appears essential for the prevention strategy.

The first lecture in the subsequent session was given by Dr. Shazib Pervaiz (Singapore) on regulation of mitochondrial respiration by the anti-apoptotic protein in Bcl-2. A model was proposed whereby overexpression of Bcl-2 promotes cell survival not only by blocking mitochondrial permeabilization and egress of death amplifying factors, but also by maintaining cellular metabolism and permissive levels of intracellular ROS that do not overwhelm the cellular antioxidant defense systems. The final lecture was by Dr. Santasree Majumdar (India) whose studies showed that theaflavin, present in tea, induces apoptosis via intracellular ROS generation in human ovarian cancer cells.

These scientific sessions were followed by a gala dinner, hosted and organized by Dr. M.S. Kanthimathi (Malaysia) in which many colourful presentations were given by participants present at the meeting. Awards were also presented for the posters, sponsored by SFRR-Malaysia and 'Free Radical Research' (see below for winners).

July 12, 2009

Session IV Oxidant signaling

The first lecture was given by Prof. Masayasu Inoue (Japan) on the mitochondrial theory of carcinogenesis and chemotherapy. His studies indicate that mitochondria are a primary site of action for DNA-targeting anticancer agents and that, in addition to GP 170-related ABC transporters, low density of mitochondria participates in the strong resistance of cancer cells to a variety of DNA-targeting anticancer agents. The next lecture by Dr. M. Betül Yerer-Aycan (Turkey) on mitochondrial electron transport chain and antioxidant defense mechanisms, with circadian rhythm alterations in rat brain and eye. These studies indicate that physiological levels of melatonin have a crucial role in the maintenance of homeostasis and antioxidant defense systems within the mitochondria, which might be important for the aging process and apoptosis. Dr. Hye-Kyung Na (Korea) then presented data on how ROS mediates 4-hydroxyestradiol-induced anchorage independent growth of human mammary epithelial cells through activation of NFκB signaling. Subsequently, Dr. Salmaan H-Inayat-Husain (Malaysia) gave a talk on styryllactone-induced apoptosis. These data provide insights into the mechanisms of goniothalamin induced apoptosis which may have important implications in the development of novel cytotoxic drugs from styryl lactones which are especially effective in killing different tumor cell lines including leukemia cells. The next lecture was by Dr. Gautham Sethi (Singapore) on targeting NFκB by celastrol, a quinone methide triterpenoid, which is used to treat cancer and chronic inflammatory and autoimmune diseases, but whose mechanism is not well understood. The present studies suggest



Figure 1. Photograph showing SFRR-Asia, SFRR-Japan and Informa Healthcare young investigator award winners along with SFRR-Asia and SFRR-International past and present Executive Committee members.

First row (sitting, left to right) Jeremy Wong Weng-Yew, Inas Almazari, Mika Jikumaru, Ling Lai Teng, Ahmad Nazrun bin Shuid, Kunishige Onuma.

Second row (standing, left to right) Michael Davies, Toshikazu Yoshikawa, T. Paul A. Devasagayam, Young-Joon Surh, Helmut Sies, Yuji Naito, Yasmin Yusof

that celastrol potentiates TNF-induced apoptosis and inhibits invasion through suppression of the NF κ B pathway.

After a tea break, three further lectures were presented. The first by Dr. Mi-Kyoung Kwak (Korea) was on Nrf as a molecular target for the cytoprotection against oxidative damage. These data suggest that Nrf2 contributes to protection against oxidative damage, and the development of pharmacological interventions that activate the Nrf2-antioxidant system might be a strategy to attenuate oxidative stress-associated human diseases. Dr. Chang Chen (China) then presented data on the repression of nuclear export by S-nitrosylation of karyopherin CRM-1 a major receptor for classical protein export. The authors speculate that this is important for promoting a cytoprotective transcriptional response to nitrosative stress. The final lecture in this session was delivered by Dr. Junichi Fujii (Japan) on how peroxiredoxin 4 deficiency causes oxidative stress-induced spermatogenic cell death. These data suggest that Prx4, most likely in the membrane bound form, is important for spermatogenesis, but not an absolute requisite.

Session V. Clinical Research & SFRR-Asia Young Investigator award

The 'clinical research' part of this session was chaired by Prof. Toshikazu Yoshikawa (Japan) and Dr. T.P.A. Devasagayam (India). The first lecture by Dr. Ah-Ng Tony Kong (USA) was on personal genomics, nutrition and cancer. His talk indicated that understanding personalized responses to dietary food factors, nutrition and cancer would require a greater integration of nutrigenomics, proteomics and metabolomics. The next lecture by Dr. An-Sik Chung (Korea) was on how selenium induces apoptosis and blocks tumor invasion. His studies suggest that selenium compounds may be useful in the prevention and treatment of cancer. The final lecture in this section was by Dr. Malyn Chulasiri (Thailand) on free radical quenching by myrobalan. These studies suggest that this product is a potential anti-ageing candidate for cosmeceuticals.

SFRR-Asia Young Investigator award session

This session contained 6 oral presentations selected by the SFRR-Asia committee from over 110 submitted abstracts by young investigators. The first presentation

was by Mika Jikumaru (Japan) on role of estrogen and nitric oxide in the sex difference of fat metabolism and survival during fasting. The second was by Ahmad Nazrun Shuid (Malaysia) on how tocotrienol supplementation improves bone structure and strength of normal male rats. The third was by Kunishige Onuma (Japan) on progression of regressive tumor cells into malignant ones by nano-scaled particles of titanium dioxide through generating ROS. The fourth one was by Ling Lai Teng (Malaysia) on how the rind of the rambutan, *Nephelium lappaceum*, is a potential source of anti-ulcer agents and antioxidants. The next one was by Jeremy Wong Weng Yew (Malaysia) on palm tocotrienol-induced suppression of tumor formation via the attenuation of angiogenesis. The final presentation was by Inas Almazari (Korea) on the anti-inflammatory and antioxidative effects of guggulsterone in human mammary epithelial cells.

Closing ceremony

The closing ceremony was hosted by Dr. Yasmin (Malaysia). Prof. Helmut Sies (Germany) provided a lucid overview of the highlights of the conference. It was announced that the next SFRR-Asia biennial meeting will be held at Kagoshima (Japan) in 2011, with the contact person being Prof. H. Majima, who invited all participants to attend. The Young Investigator awards were presented, on behalf of SFRR-Asia, by the Secretary-General, Prof. Y. Naito, and President, Dr. Devasagayam. The award winners were:

Informa Healthcare Young Investigator Awards (Oral):

Ahmad Nazrun bin Shuid (Universiti Kebangsaan Malaysia, Malaysia)
Ling Lai Teng (Universiti of Malaya, Malaysia)

SFRR Asia Awards 2009 (Oral):

Jeremy Wong Weng-Yew (Malaysian Palm Oil Board, Malaysia)

Mika Jikumaru (Osaka, Japan)
Inas Almazari (Seoul National University, Seoul, Korea)

SFRR Japan Young Investigator Award (Oral):

Kunishige Onuma (Yamagata University, Japan)

Informa Healthcare Prestigious Poster Awards:

Amlan Das (University of Calcutta, India)
Shin-Ru Lin (Chang Gung University, Taiwan)

SFRR-Malaysia Poster Awards:

Amlan Das (University of Calcutta, India)
Chandramathi Raju (Universiti Malaya, Malaysia)
Helmant Poudyal (University of Queensland, Australia)
Noramlizan Ramli (Universiti Teknologi Malaysia, Malaysia)
Shailah Abdullah (Universiti Kebangsaan Malaysia, Malaysia)

Apart from the scientific sessions described above there was also a pre-conference workshop held on 8th July on the theme of *Apoptosis: Mechanism of Cell Death & Therapeutic Implications*, held at the Concorde Hotel, Kuala Lumpur, Malaysia.

I take this opportunity to thank the organizers, sponsors, SFRR-Asia executive committee members and the editorial board and publishers of 'Free Radical Research' (Informa Health Care) for their help and support, and for making this conference a successful event.

Dr. T.P.A. Devasagayam

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