

Open Access Article

The authors, the publisher, and the right holders grant the right to use, reproduce, and disseminate the work in digital form to all users.

Technology in Cancer Research and Treatment

ISSN 1533-0346

Volume 7, Number 4, August 2008

©Adenine Press (2008)

Latest Discoveries and Trends in Translational Cancer Research: Highlights of the 2008 Annual Meeting of the American Association for Cancer Research

www.tcrt.org

William C. S. Cho, Ph.D.

Department of Clinical Oncology
Queen Elizabeth Hospital
Hong Kong SAR, PR China

The Annual Meeting of the American Association for Cancer Research (AACR) is the world's largest and most comprehensive gathering of cancer researchers. At the 2008 AACR Annual Meeting, innovative research approaches, novel technologies, potentially life-saving therapies in the pipeline, late-breaking clinical trial findings, and new approaches to cancer prevention were presented by top scientists. Reflecting the global state of cancer research with an eye toward future trends, several areas of great science and discovery in the cancer field were shared in this report, which include cancer biomarkers, the role of microRNAs in cancer research, cancer stem cells, tumor microenvironment, targeted therapy, and cancer prevention. This article presents an overview of hot topics discussed at the 2008 AACR Annual Meeting and recapitulates some scientific sessions geared toward new technologies, recent progress, and current challenges reported by cancer researchers. For those who did not attend the meeting, this report may serve as a highlight of this important international cancer research meeting.

Key words: Cancer biomarkers; MicroRNAs; Cancer stem cells; Tumor microenvironment; Targeted therapy; and Cancer prevention.

Introduction

More than 17,000 cancer researchers from 60 countries gathered in the 2008 Annual Meeting of the American Association for Cancer Research (AACR) in San Diego held on April 12-16 to discuss around 6,000 abstracts and to hear more than 500 invited presentations on new and significant discoveries in basic, translational, and clinical cancer research. The theme for the 2008 AACR Annual Meeting is "Translating the Latest Discoveries into Cancer Prevention and Cures." Scientific program (plenary sessions, symposia, forums, meet-the-expert sessions, new concepts in organ site research sessions, etc.), scientific award lectures, methods workshops, networking events, and educational sessions rounded out the comprehensive program. This article presents an overview of hot topics discussed at the 2008 AACR Annual Meeting and reviews some scientific sessions geared toward new technologies, recent progress, and current challenges reported by cancer researchers.

Cancer Biomarkers

There has been much interest in biomarkers of cancer risk in predicting future patterns of disease, especially as cancer treatment has made such positive strides in the last few years using various *omics* approaches (1-4). However, a survey

*Corresponding Author:
William C. S. Cho, Ph.D.
Email: choecs@ha.org.hk

of the 10 largest pharmaceutical companies conducted between 1991 and 2000 showed that the overall failure rate for oncology drugs was 40% during phase I, 70% during phase II, 60% during Phase III, and of the few showing success in phase III 30% were not approved (5). Unfortunately, there are few tools available that enable “quick to kill” and “quick to proof of concept” decisions to be made during the early phases of drug development. The hope is that by identifying tumors that are dependent upon the targeted pathways and by demonstrating that the drug modulates the pathway, it will be possible to identify the right patients for the pivotal trials and hence significantly increase the probability of success (6).

Professor Workman (7) also emphasized that utilizing well-chosen biomarkers in the preclinical drug discovery and development phase can facilitate the optimization of pharmacokinetic, pharmacodynamic, and therapeutic properties for clinical evaluation. He gave some examples from his drug discovery projects in a symposium, including the development of potential therapeutic agents acting on the 4,5-dia-rylisoxazole HSP90 molecular chaperone inhibitors (8) and the pharmacologic characterization of a potent inhibitor of class I phosphatidylinositol 3-kinase (PI3K) (9).

Another mitogenic extracellular kinase 1/2 (MEK1/2) inhibitor, PD0325901, is deemed to have potent activity on cells harboring gain-of-function mutations of the *BRAF* gene and to a lesser extent, wild-type and *RAS* family members *in vitro*. Using the SKMEL-28 and HCT116 (with endogenous activating mutation in *KRAS*) tumor-bearing mice models, Leyton *et al.* find that 3'-deoxy-3'-[¹⁸F]fluorothymidine positron emission tomography is a sensitive early cognate pharmacodynamic biomarker for MEK1/2 tumor growth inhibition in tumors with or without mutation in the *BRAF* gene (10).

Yaguchi *et al.* also developed a novel PI3K inhibitor, ZSTK474, which has strong antitumor activity and low toxicity (11). They established a useful methodology to identify drug-sensitive phosphoproteins by the combined use of immobilized metal affinity chromatography and surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS), and identified phosphorylated 4E-binding protein 1 as a ZSTK474-sensitive protein that might be a biomarker to predict therapeutic efficacy of ZSTK474 (12).

The tumor specific alterations in protein glycosylation on the cell surface and in body fluids might be potential targets for new cancer diagnostics and therapeutics. Also, using SELDI-TOF MS followed by matrix-assisted laser desorption/ionization quadrupole ion trap TOF MS/MS analysis, Ueda *et al.* reported that their novel glycoproteomic approach has identified a carbohydrate-targeting serum tumor marker Apolipoprotein C-III for lung cancer using lectin-coupled proteinchip system (13).

The clinical use of small molecule tyrosine kinase inhibitors (TKI) such as gefitinib and erlotinib against epidermal growth factor receptor (EGFR) represented a major breakthrough in lung cancer treatment. However, standard DNA sequencing is either not sensitive enough or too labor-intensive. Wang *et al.* adopted a mutation-specific digital-polymerase chain reaction using a new nanofluidic platform, the digital array for quantitative detection of clinically relevant massively diluted mutated alleles of EGFR and MET kinase at the single-cell level with a sensitivity of at least 0.04% (14).

Another challenge is to identify the sub-populations that will respond to prescribed targeted therapies through biomarkers and surrogate endpoints. The findings of Yonesaka *et al.* suggest that the presence of amphiregulin autocrine-loop predicts the *in vitro* sensitivity of *EGFR* wild type non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (SCC) cell lines to gefitinib and cetuximab. Amphiregulin expression may be a suitable biomarker to select *EGFR* wild type NSCLC patients likely to benefit from gefitinib or erlotinib (15).

Aiming to preserve a functional larynx, concomitant chemoradiation became the gold standard for treatment of locally advanced SCC of the larynx. However, non-responders suffer from high morbidity and delay in salvage surgery. Using mRNA for gene expression profiling, Barreto *et al.* identified the genes *IL4R* and *MET* were over regulated in the responders while *NTRK2*, *EGFR*, *GNA12*, and *TGFA* were over regulated in the non-responders. Their data demonstrates that molecular classifiers can be applied to select patients for chemoradiotherapy or surgical treatment of locally advanced SCC of the larynx (16).

On the other hand, HER-2 (a member of the EGFR family) is overexpressed in ~25-30% of invasive breast cancers and correlates with a poor prognosis and aggressive disease. Leshniak *et al.* showed that overexpression of β 1-integrin membrane staining by immunohistochemistry was an independent prognostic marker of time to tumor progression and overall survival. Their preclinical data support that inhibition of β 1-integrin can convert trastuzumab (a humanized antibody that binds to HER-2) resistance to the sensitive phenotype *in vitro* and *in vivo* models. Their findings strengthen the rationale to use β 1-integrin in conjunction with HER-2 as predictive biomarkers of trastuzumab resistance (17).

Nevertheless, achieving a permanent cure by eradicating metastatic breast cancer is still elusive. While Homeobox B7 (*HOXB7*) is overexpressed in approximately 30% of primary breast cancers and to greater extent in bone metastases, Sukumar *et al.* suggest that patients whose breast tumors overexpress *HOXB7* and are resistant to treatment with tamoxifen may be responsive to sequential treatment with the

aromatase inhibitors. In their molecular studies of metastasis facilitated by a rapid autopsy program, the TKI gefitinib and Arbeitsgemeinschaft Erneuerbare Energie (Novartis) inhibited MCF-7-*HOXB7* cell proliferation. The mTOR inhibitor RAD-001 (Novartis) was also found to be an effective inhibitor of *HOXB7* cells at low nM concentrations (18).

For late-stage ovarian cancer, the availability of reliable molecular markers to predict intrinsic and drug-induced cisplatin resistance in these cancer cells presents an enormous opportunity to individualized treatment for resistant patient sub-population. Using an MS based proteomics approach, Aggarwal *et al.* showed that expression of the immune modulators CD70 and B7-H2 was associated with cisplatin resistance in ovarian cancer (19).

The Role of MicroRNAs in Cancer Research

Recognition of the importance of small non-coding RNAs in recent years catalyzes the enthusiasm to explore the role of microRNAs (miRNAs) in cancer research (20). One of the oral presenters for the opening plenary sessions, Professor Phillip Sharp of Massachusetts Institute of Technology, an American geneticist and molecular biologist who co-discovered split genes and RNA splicing that won the 1993 Nobel Prize in Physiology or Medicine, gave a talk on the biology of short RNAs in context of cancer. Professor Sharp described how mutations that alter the activities of miRNAs can impact on the properties of tumor cells and the rate of development of cancers. Short RNAs can control expression of genes at the stage of suppression of transcription in many organisms. The evidence for this type of regulation in vertebrate organisms is incomplete, but the recently discovered PIWI-interacting RNAs (piRNAs) expressed in the paternal and maternal germlines of mammals may mediate such regulation. The activity of short interfering RNAs (siRNAs) transfected into mammalian cells is the result of their incorporation into the miRNA pathway that is active in all cell types. The siRNAs can be designed to treat cancer by targeting the silencing of genes controlling cell growth, oncogenes, or cell death (21).

The *RAS* family makes up major oncogenes in various cancers. Professor Slack showed that *let-7* is highly expressed in lung tissue and that inhibiting *let-7* function leads to increased cell division in A549 lung cancer cells, providing evidence that *let-7* functions as a tumor suppressor in lung cells. Over-expression of *let-7* in cancer cell lines alters cell cycle progression and reduces cell division. His work reveals the *let-7* miRNA to be a master regulator of cell proliferation pathways (22).

TEL-AML1 is the most common gene lesion in childhood leukemia. Diakos *et al.* observed an up-regulation of *miR-494* and *miR-320* upon *TEL-AML1* silencing. They demon-

strated that survivin is a target of these miRNAs. Their data suggest that *TEL-AML1* might exert its anti-apoptotic action at least in part by affecting *miR-494* and *miR-320* expression and their target survivin (23).

Prostate-derived Ets factor (PDEF) is an Ets transcription factor with expression restricted to tissues with high epithelial content, including breast, prostate, and colon. Findlay *et al.* showed that expression of *miR-204* and *miR-510* are elevated in human breast tumor samples compared to matched non-tumor samples. Their study provides a mechanism for the loss of PDEF protein expression and a unique oncogenic role for these miRNAs during metastatic breast cancer progression (24).

Breast cancer metastasis suppressor 1 (*BRMS1*) suppresses metastasis of multiple carcinomas without blocking tumorigenesis. However, the exact mechanism of *BRMS1* metastasis suppression is still not known. Recent work by Edmonds *et al.* reported that *BRMS1* transfection decreases *EGFR*, *Twist1*, and *miR-10b* expression. Given the relationships between these molecules, a regulatory pathway of *BRMS1* → *EGFR* → *Twist1* → *miR-10b* is suggested (25).

Cancer Stem Cells

Cancer stem cells (CSCs), being the mutated counterparts of normal stem cells, may have similar functions as normal stem cells that are naturally resistant to chemotherapeutic agents. These surviving cancer stem cells can repopulate the tumor, which causes relapse and metastasis. There have been some researches finding specific biomarkers to distinguish cancer stem cells from normal cells (as well as from normal stem cells) reported in the 2008 AACR Annual Meeting.

As a number of CSCs are resistant to radiation and chemotherapy, complete elimination of these cells from the tumor mass determines therapeutic success. Vlashi *et al.* reported a novel marker that allows identification of CSCs in breast cancer and glioma *via* low 26S proteasome activity. Cell lines infected with reporter constructs for proteasome activity can be utilized to identify CSCs and track their response to cancer treatments. This feature can be exploited as a specific target for selective elimination of CSCs, leading to improved tumor control (26).

There was a report on new approaches to biological therapy. Fieger *et al.* demonstrated that the anti-B7-H3-4Ig monoclonal antibody TES7 recognizes cancer stem cell lines, modulates angiogenic factor secretion, and exhibits potent anti-tumor activity *in vivo*. The treatment of prostate tumor stem cell SRC xenografts, with TES7 significantly reduces the secretion of vascular endothelial growth factor (VEGF) up to 60% in a subset of the tumor stem cell lines, suggesting that

regulation of VEGF may contribute to the anti-tumor activity of TES7 observed *in vivo* (27).

On the other hand, Yasuda *et al.* performed methylation specific polymerase chain reaction to evaluate the methylation status and found that some of the genes, such as *p16*, *ESR1*, and *RAR β* , were unmethylated only in cancer stem-like cells, while those were fully methylated in the rest of cancer cells. It suggests that the generally accepted concept of aberrant promoter DNA hypermethylation in cancer cells cannot be applied to cancer stem-like cells and also indicates that DNA demethylating agents may not be able to fully eradicate the cancer stem like-cells (28).

Kim *et al.* reported that targeted disruption of signal transducer and activator of transcription STAT3 in bulge region keratinocyte stem cells inhibits chemically-induced skin carcinogenesis. They showed that STAT3 is required for both the initiation and promotion stages of skin carcinogenesis (29).

During embryonic development, conserved signaling pathways such as Hedgehog (Hh), Wingless, and Notch precisely regulate critical cellular processes (*e.g.*, self-renewal and differentiation). Studying the expression of the Hh signaling in human B-precursor acute lymphocytic leukemia (ALL) cell lines, Lin *et al.* found that colony-formation was significantly inhibited by cyclopamine and IPI-926. Their results suggest that the inhibition of Hh signaling impairs ALL self-renewal by targeting a rare cell population which may be responsible for disease propagation (30).

CD133-positive CSCs in glioblastoma (GBM) were recently shown to be resistant to commonly used chemotherapy and radiotherapy (31, 32). Fan *et al.* depleted CSCs by Notch pathway blockade inhibits tumor growth and propagation both *in vitro* and *in vivo*. Reduced expression of phosphorylated Akt and STAT3 in these GBM neurosphere cells after gamma-secretase inhibitor GSI-18 application suggests that Notch pathway inhibition depletes CSCs through Akt/STAT3 mediated apoptosis. The results suggest that GSIs can be used as chemotherapeutic reagents to target CSCs in malignant brain tumors (33).

Ginestier *et al.* utilized Reparixin, a small molecule inhibitor of IL8 signaling, to show that the IL8/CXCR1 pathway plays an important role in the regulation of breast CSCs. The IL8 is produced by a variety of inflammatory and stromal cells suggesting a link between microenvironment and cancer involving this pathway. Inhibition of this pathway may provide a novel therapeutic approach to target breast CSCs (34).

On the other hand, Rasheed *et al.* evaluated aldehyde dehydrogenase (ALDH) expression in primary pathologic specimen from 268 patients with pancreatic cancer by immu-

nohistochemistry. They found that CD44⁺CD24⁺ALDH⁺ cells isolated from tumor xenografts have significantly lower expression of E-cadherin and higher expression of Slug, a transcriptional repressor of E-cadherin, compared to ALDH⁺ or ALDH⁻ cells. Therefore, ALDH appears to mark highly clonogenic pancreatic CSCs. Moreover, increased features associated with epithelial-to-mesenchymal transition may play a role in the correlation of ALDH⁺ cells with long-term outcomes (35).

Recent discoveries have given rise to the theory that fusion events between stem cells and tumor cells could act as malignant and crucial originators in CSC generation. Schwitalla *et al.* co-cultured breast stem cells with breast cancer cells. The finding that breast stem cell/breast cancer cell hybrids exhibit a higher proliferative activity and increased expression levels of drug resistance transporters indicates that such fusion events may contribute to tumor progression and possible to the evolution of a CSC phenotype (36).

Though large volume of works has been done on CSCs, it is envisioned that the purification of CSC will be followed by the characterization of mutations, chromosomal aberrations, active signaling pathways, and unique surface antigens. This knowledge will guide the development of highly specific and more effective anti-cancer therapies.

Tumor Microenvironment

The microenvironment in which a tumor originates plays a crucial role in cancer initiation and progression. Recent studies indicate that the tumor microenvironment is unique in providing both supportive and inhibitory factors which determine the fate of the tumor and its host. Some reviews of studies from experts in the field were provided in the 2008 AACR Annual Meeting.

Epithelial-mesenchymal transition (EMT) is a dynamic trans-differentiation process to acquire cell mobility for body organization. Kudo-Saito *et al.* established a human pancreatic cancer cell line (Panc-1) transduced with *Snail* gene, which is an essential transcription factor governing EMT. They demonstrated that *Snail* expression in tumor cells induces the immunosuppressive microenvironment involving impaired dendritic cells (DC) and regulatory T cells, resulting in promotion of tumor metastasis. Blockade of the molecules identified is effective in simultaneously suppressing both tumor metastasis and immunosuppression (37).

Clinical observations suggest that shedding of the MHC class I chain-related molecule (MIC), a ligand of NKG2D, might be one of the mechanisms by which tumors evade host immune surveillance and progress. Wu *et al.* overexpressed the wild-type membrane integrated MICB, the extracellular do-

main secretable sMICB, and a mutated non-cleavable MICB. A2 forms of human MICB in mouse TRAMP-C2 prostate tumor cells. They showed that MIC shedding may contribute significantly to tumor formation by transformed cells and that inhibition of MIC shedding to sustain the NKG2D receptor-MIC ligand recognition may have potential clinical implication in targeted cancer treatment (38).

The IL-15 is a proinflammatory cytokine, as it induces the production of cytokines, which plays a role in various inflammatory processes. A correlation was observed by Badoual *et al.* between ADAM-17 expression in tumor cells and serum sIL-15R α concentrations in head and neck cancer patients. Tumor cells coexpress IL-15R α and ADAM-17 *in vivo*. However, sIL-15R α did not act *in vitro* as an IL-15 antagonist but rather as an enhancer of IL-15-induced proinflammatory cytokines (IL-6, TNF α , IL-17) that may promote tumor progression (39).

To identify causative molecules that promote the susceptibility of human colorectal cancer cells, Ueda *et al.* examined the expression of a panel of proteins that are known to mediate cytotoxic T lymphocytes-tumor cell interactions. Their results suggest that Dicer is responsible for the generation of *miR-222* and *miR-339*, which suppress intercellular adhesion molecule-1 expression on cancer cells, thereby down-regulating the susceptibility of cancer cells to cytotoxic T lymphocytes-mediated lysis (40).

Curtin *et al.* uncovered a novel pathway for the activation of GBM antigen-specific T-cell dependent immune response, which is mediated by the release of the high-mobility-group box 1 (HMGB1) by dying tumor cells after treatment with thymidine kinase together with ganciclovir and this can induce toll-like receptor 2 (TLR2) signaling in DC. Their results indicate that endogenous TLR2 signaling induced by HMGB1 promotes CD8 $^+$ T cell dependent anti-GBM immune responses that result in tumor regression *in vivo* (41).

Apoptotic and necrotic cells expose phosphatidylserine (PS). Annexins are characterized by the ability to bind phospholipids of membranes in the presence of Ca $^{2+}$. Frey *et al.* demonstrated that the disturbed PS-dependent clearance by macrophages of apoptotic cells leads to the accumulation of the latter and to the occurrence of secondary necrotic cells. Danger signals are released by the secondary necrotic cells, which have lost their membrane integrity. The immunity against apoptotic cells can be increased by blocking the PS-dependent clearance with Annexin A5 (42).

Differentiation of DC crucially depends on the micro-environment. Novitskiy *et al.* found that adenosine signaling through A $_{2B}$ receptor is an important factor of aberrant DC differentiation leading to generation of tolerogenic, angiogenic, and pro-inflammatory DC. Generation of these

adenosine-differentiated DC would have an adverse effect in cancer and inflammatory diseases through a process that could be prevented by A $_{2B}$ antagonists (43).

One phenotype of myeloid suppressor (CD14 $^+$ /HLA-DR $^-$) is associated with adverse response to sepsis and has been identified in patients with advanced melanoma. Lin *et al.* showed that these CD14 $^+$ /HLA-DR $^-$ cells could affect both the adaptive immune response *via* inhibition of DC differentiation and the effector immune response by interfering with T cell proliferation (44).

The TLR agonists critically regulate immune responses by virtue of specialized receptors in DC. Xu *et al.* demonstrated that DC activated by single TLR agonists secreted IL-23 with no or little IL-12, favoring a Th17 polarized inflammatory response. Dual TLR agonists (R848 and LPS) or IFN- γ and LPS generate DC that produce IL-12 and IL-23, favoring anti-tumor immunity. These results have important implications for balancing chronic inflammation long known to promote tumor development against anti-tumor immunity (45).

The IL-12 is a strong anti-tumor immune mediator and hardly detectable in tumor, whereas IL-23 suppresses anti-tumor immunity and is highly expressed in cancer. Kortylewski *et al.* demonstrated that STAT3 is critical for IL-23 over-expression in tumor and IL-23 in turn helps to propagate immunosuppressive effects of STAT3 activity from tumor stromal myeloid cells to DC and tumor T regulatory cells. Targeting STAT3-IL-23 within the tumor microenvironment may overcome tumor immune evasion (46).

Hypoxia is a distinctive microenvironment for tumors that are rapidly growing. In the tumor tissue under hypoxia, a transcription factor hypoxia-inducible factor 1 (HIF-1) α plays a critical role in regulating expressions of various genes associated with tumor progression. Teramoto *et al.* demonstrated that hypoxia in the tumor tissue is associated with an immunosuppressive cytokine TGF- β -mediated immunosuppression and HIF-1 inhibitors can improve anti-tumor immune responses in tumor-bearing hosts (47).

Silencing of tumor suppressor genes mediated by epigenetic modifications of the cancer genome is an area of intense research; however, the causative mechanisms triggering this mode of gene silencing remain unclear. Zuo *et al.* indicated that the silencing of a putative tumor suppressor gene *CST6* correlated with the activation of Akt signaling pathway in mammary epithelial cells when they were in contact with cancer associated fibroblasts. In addition, they observed repressed chromatin marks in the promoter of *CST6* in breast epithelial cells transfected with Mry-Akt1 cDNA further implicating the activation of Akt signaling pathway in the epigenetic silencing of *CST6* (48).

The TGF β is a very important tumor suppressor. Inactivation of TGF β signaling frequently occurs in human cancers and contributes to tumor metastasis. Yang *et al.* showed that Gr-1⁺CD11b⁺ myeloid cells infiltrate into the invasive front of tumor tissues, and facilitate tumor cell invasion and metastasis through a process involving metalloproteinase activity. This infiltration of Gr-1⁺CD11b⁺ cells also results in increased abundance of TGF β 1 in tumors with Tgfr2 deletion. Thus, the tumor-suppressing role of TGF β can be switched to tumor promoting through the recruitment of Gr-1⁺CD11b⁺ cells in the tumor microenvironment (49).

The mechanisms by which stromal cells remodel the tumor extracellular matrix are poorly understood. Perentes *et al.* showed that the matrix-modifying hormone relaxin reorganizes the collagen network, inhibits tumor associated fibroblasts (TAFs) migration in tumors and increases TAF interaction with collagen fibers by inducing the expression of beta 1-integrin. The TAF induced changes in the collagen network are mediated by matrix metalloproteinases (MMPs). In contrast, untreated tumors maintained a relatively stable collagen network. They found that direct contact between slowly moving or stationary TAFs and collagen fibers *via* beta 1-integrin is a key mechanism of matrix MMP-mediated collagen remodeling *in vivo* (50).

Constitutive increases in prostaglandin production are associated with initiation and progression of several types of cancers. Based on their studies, Weiser-Evans *et al.* proposed that in addition to having direct effects in NSCLC, cytosolic phospholipase A₂ (cPLA₂) plays an important role in the tumor microenvironment, specifically the macrophage. They hypothesized that cPLA₂ is critical for mobilization of macrophages to the tumor and may play a critical role in cytokine production required for lung cancer progression and metastasis (51).

Targeted Therapy

Targeted therapies have significantly changed the treatment of cancer over the past decade. As many oncologists believe that targeted therapies are the chemotherapy of the future, new approaches for more tumor specific treatment with less toxicity continue to be investigated.

The *Bcl-2* proto-oncogene is overexpressed in 50-70% of breast cancers, potentially leading to resistance to chemotherapy, radiation, and hormone therapy. Ozpolat *et al.* demonstrated that targeted silencing of *Bcl-2* induces autophagic cell death which is mediated by ATG5 in breast cancer cells and that induction of autophagic cell may be used as a therapeutic strategy alone or in combination with chemotherapy death in breast cancer cells overexpressing *Bcl-2* (52).

Mammalian target of rapamycin (mTOR) plays a central role in regulating cell growth and cell cycle progression. Santiskul-

vong *et al.* found that in the LSL-*K-Ras* G12D/+/*PTEN* loxP/loxP murine ovarian cancer model that is based on conditional deletion of the tumor suppressor gene *PTEN* and concomitant expression of constitutively active *K-Ras*, oral administration of either the mTOR inhibitor RAD001 or the dual pan-PI3K/mTOR inhibitor NVP-BEZ235 resulted in significantly reduced S6 ribosomal protein phosphorylation for RAD001, and decreased Akt phosphorylation for NVP-BEZ235 in tumor tissue of treated mice. Their results indicated that the efficacy of mTOR inhibition can be significantly enhanced by concomitant inhibition of Akt phosphorylation (53).

Using a TKI-sensitive NSCLC cell line, Sharma *et al.* isolated several clones with striking resistance (500-fold) to EGFR-TKIs. The TKI resistance in these clones is completely reversible over time, suggesting a non-mutational and possibly epigenetic mechanism in mediating cell survival. This *in vitro* model recapitulates the clinical experience of reversible resistance experienced by some NSCLC patients. This mechanism of drug resistance (or more appropriately designated drug tolerance) allows the tumor cells to evade the initial onslaught of the drug and allow a small fraction of cancer cells to persist long enough until more permanent, genetic forms of drug resistance can develop (54).

Investigating how to overcome the biologic heterogeneity on resistance to treatment, Kuwai *et al.* revealed that oral AEE788 (an inhibitor of EGFR phosphorylation) suppressed proliferation and increased apoptosis of tumor cells and tumor-associated endothelial cells. Oral STI571 (an inhibitor of platelet-derived growth factor receptor β phosphorylation) increased apoptosis of tumor-associated endothelial cells and pericytes. The combination of AEE788, STI571, and irinotecan produced the greatest inhibition of primary tumor growth and metastasis (55).

Although the cross-talk between EGFR and endothelin A receptor (ET_AR) generates signaling networks that confer an aggressive phenotype to ovarian cancer cells, the underlying mechanisms that follow ET_AR ligand binding remain unknown. Rosano *et al.* showed that β -arrestin-1 siRNA inhibited β -catenin transcriptional activity and cell invasion, indicating that β -arrestin-1 is a necessary component for endothelin-1-induced EMT-related signaling. Both ZD4054, a specific ET_AR antagonist, and ET_AR siRNA prevented the signalplex formation and EGFR transactivation, impairing the signaling network involved in EMT (56).

The availability of advanced tools would impact dramatically the efficiency and development speed of targeted therapies (57). Concurrent chemoradiotherapy has been proven efficaciously superior to sequential therapy, but it also significantly increases toxicity. Nanoparticle formulations of chemotherapy have been shown to increase efficacy and decrease toxic-

ity when compared to small molecule counterparts. Wang *et al.* developed a novel targeted nanoparticle platform that can carry both chemotherapeutics and metal radioisotopes, making nanoparticle delivery of concurrent chemoradiotherapy possible. This platform can also be used for dual imaging and therapy when an imaging radioisotope is used (58).

Cancer Prevention

Many epidemiological studies have demonstrated an inverse quantitative relation between the consumption of supplementations or plant-based diets and the risk of developing a variety of cancers. Some reviews were reported in the 2008 AACR Annual Meeting to reveal the protective properties of these substances.

Several lines of evidence suggest that higher calcium intake and higher vitamin D status have anti-neoplastic effects, this is most apparent for colorectal carcinogenesis. Animal studies have consistently shown that higher calcium intake reduces the risk of experimental large bowel tumors, and there are similar findings for vitamin D and its analogues. There is also evidence that there may be an interaction of calcium and vitamin D in their anti-neoplastic effects, at least in the large bowel. Thus, calcium and vitamin D may work synergistically through the same biological pathways in inhibiting the development of colorectal neoplasia (59).

There is substantial evidence that the very high concentrations of glucosinolates (GS), secondary phytochemicals present in the seeds, sprouts, and mature forms of *Cruciferae*, play a major role in the protective effects on cancers. Many of the effects of GS on animal tissues are almost certainly not due to the GS themselves but to their isothiocyanate (ITC) and other enzymatic hydrolysis products. However, the efficiency of the GS to ITC conversion varies enormously among individuals (from 2% to 40%). Differences in bioavailability of ITC from GS among individuals may vary the protective efficacy of crucifers (60).

The cancer preventive activities of many polyphenols have been demonstrated in different animal models. However, epidemiological studies did not convincingly demonstrate a reduction of human cancer risk associated with the consumption of flavanols (such as quercetin and myricetin found in many vegetables, fruits, and beverages) and anthocyanins (such as glycosides of cyanidin and delphinidin found in berries, grapes, cabbages, onions, radishes, etc). More studies on their bioavailabilities and mechanisms of actions are needed to bridge the gaps between animal and human studies (61).

Epidemiologic studies suggest a 20-40% reduction in the risk of colorectal cancer and adenomas in individuals with high folate intake compared with those with low intake. However,

based on the lack of compelling supportive evidence and on the potential tumor-promoting effect, routine folic acid supplementation is not recommended as a chemopreventive measure against colorectal cancer and other cancers (62).

Afterthought

This year's AACR Annual Meeting is at a crossroad. Inheriting the 2007 Centennial Meeting (63) and breaking new grounds for the future, cancer researchers are making breakthroughs that are giving cancer patients new hope. The friendly ambience of the meeting stimulated much discussion and cross fertilization of ideas between the participants that will surely lead to further exciting new developments in cancer research. Leading scientists are using novel approaches to detect cancer early and studying the first potential therapeutic agents aimed at launching cancer prevention and halting cancer progression. With effective treatments just over the horizon, we can see the beginning of the end for cancer.

Conflict of Interest Statement

None declared.

References

1. Cho, W. C. Contribution of oncoproteomics to cancer biomarker discovery. *Mol Cancer* 6, 25 (2007).
2. Cho, W. C., Cheng, C. H. Oncoproteomics: current trends and future perspectives. *Expert Rev Proteomics* 4, 401-410 (2007).
3. Cho, W. C. Proteomics technologies and challenges. *Genomics Proteomics Bioinformatics* 5, 77-85 (2007).
4. Cho, W. C. Cancer biomarker discovery: the contribution of "Omics". *BIOforum Eur* 11, 35-37 (2007).
5. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Discov* 3, 711-715 (2004).
6. Clark, E. A. Incorporating tissue-based predictive biomarkers in oncology clinical trials. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract SY20-03, AACR 2008, Philadelphia, PA.
7. Workman, P. Biomarkers in drug development: hiking the pharmacologic audit trail. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract SY20-02, AACR 2008, Philadelphia, PA.
8. Brough, P. A., Aherne, W., Barril, X., *et al.* 4,5-diarylisoaxazole HSP90 chaperone inhibitors: potential therapeutic agents for the treatment of cancer. *J Med Chem* 51, 196-218 (2008).
9. Raynaud, F. I., Eccles, S., Clarke, P. A., *et al.* Pharmacologic characterization of a potent inhibitor of class I phosphatidylinositide 3-kinases. *Cancer Res* 67, 5840-5850 (2007).
10. Leyton, J., Smith, G., Lee, M. *et al.* 3'-deoxy-3'-[¹⁸F]fluorothymidine positron emission tomography is a sensitive early biomarker for tumor growth inhibition by the mitogenic extracellular kinase inhibitor PD0325901. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2579, AACR 2008, Philadelphia, PA.
11. Yaguchi, S., Fukui, Y., Koshimizu, I., *et al.* Antitumor activity of ZSTK474, a new phosphatidylinositol 3-kinase inhibitor. *J Natl Cancer Inst* 98, 545-556 (2006).
12. Akashi, T., Yaguchi, S., Okamura, M., *et al.* Phosphoproteomic screening of biomarkers for assessing response to a PI3K inhibitor

- by using SELDI-TOF MS. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2432, AACR 2008, Philadelphia, PA.
13. Ueda, K., Daigo, Y., Fukase, Y., *et al.* A novel glycoproteomic approach for the discovery of carbohydrate-targeting serum tumor markers for lung cancer using Lectin-coupled ProteinChip system. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2433, AACR 2008, Philadelphia, PA.
 14. Wang, J., Ramakrishnan, R., Tang, Z., *et al.* Quantitative detection of clinically relevant massively diluted mutated alleles of EGFR and MET kinase at single-cell level using a novel nanofluidic digital-PCR platform. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 4955, AACR 2008, Philadelphia, PA.
 15. Yonesaka, K., Zejnullahu, K., Homes, A. J., *et al.* Presence of amphiregulin autocrine-loop predicts sensitivity of EGFR wild type cancers to gefitinib and cetuximab. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 4958, AACR 2008, Philadelphia, PA.
 16. Barreto, B., Feher, O., Carvalho, A., *et al.* Molecular classifiers as predictors of responsiveness to concomitant chemoradiotherapy in SCC of the larynx. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 4142, AACR 2008, Philadelphia, PA.
 17. Lesniak, D., Sabri, S., Xu, Y., *et al.* β 1-integrin: A novel predictive biomarker and a target in HER-2-overexpressing trastuzumab resistant women with breast cancer. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 5826, AACR 2008, Philadelphia, PA.
 18. Sukumar, S., Bhujwala, Z., Brodie, A., *et al.* Molecular studies of metastasis facilitated by a rapid autopsy program. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract SY32-01, AACR 2008, Philadelphia, PA.
 19. Aggarwal, S., He, T., Fitzhugh, W., *et al.* Membrane proteomic analyses of ovarian cancer identifies the immune modulators CD70 and B7-H2 as candidate markers of cisplatin response. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2430, AACR 2008, Philadelphia, PA.
 20. Cho, W. C. OncomiRs: the discovery and progress of microRNAs in cancers. *Mol Cancer* 6, 60 (2007).
 21. Sharp, P. A. The biology of short RNAs in the context of cancer. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract PL01-03, AACR 2008, Philadelphia, PA.
 22. Slack, F. microRNAs in cell differentiation and cancer. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract SY31-01, AACR 2008, Philadelphia, PA.
 23. Diakos, C., Xiao, Y., Zheng, S., *et al.* TEL-AML1 regulates survivin and apoptosis via miRNA-494 and miRNA-320. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2507, AACR 2008, Philadelphia, PA.
 24. Findlay, V. J., Turner, D. P., Moussa, O., *et al.* MicroRNA-mediated loss of PDEF protein expression results in progression to more invasive breast cancer. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 1569, AACR 2008, Philadelphia, PA.
 25. Edmonds, M. D., Vaidya, K. S., Chen, D., *et al.* Breast cancer metastasis suppressor 1 (BRMS1) potentially suppresses metastasis by regulating microRNA expression as identified via using microRNA array and qRT-PCR. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2486, AACR 2008, Philadelphia, PA.
 26. Vlashi, E., Kim, K., Della Donna, L., *et al.* Prospective identification, tracking, and targeting of cancer-initiating cells in breast cancer and glioma via low proteasome activity. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 4997, AACR 2008, Philadelphia, PA.
 27. Fieger, C. B., Chen, F., Coberly, S., *et al.* The anti-B7-H3-4Ig antibody TES7 recognizes cancer stem cell lines, modulates angiogenic factor secretion, and exhibits potent anti-tumor activity in vivo. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2555, AACR 2008, Philadelphia, PA.
 28. Yasuda, H., Soejima, K., Naoki, K., *et al.* Several genes are evaded aberrant DNA hypermethylation in cancer stem-like cells of solid tumor. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2536, AACR 2008, Philadelphia, PA.
 29. Kim, D. J., Kataoka, K., Cotsarelis, G., *et al.* Targeted disruption of signal transducer and activator of transcription 3 (Stat3) in bulge region keratinocyte stem cells inhibits chemically-induced skin carcinogenesis. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2501, AACR 2008, Philadelphia, PA.
 30. Lin, T. L., Wang, Q., Brown, P., *et al.* Self-renewal of acute lymphocytic leukemia cells is limited by the Hedgehog pathway inhibitors cyclopamine and IPI-926. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 4999, AACR 2008, Philadelphia, PA.
 31. Bao, S., Wu, Q., McLendon, R. E., *et al.* Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature* 444, 756-760 (2006).
 32. Liu, G., Yuan, X., Zeng, Z., *et al.* Analysis of gene expression and chemoresistance of CD133+ cancer stem cells in glioblastoma. *Mol Cancer* 5, 67 (2006).
 33. Fan, X., Khaki, L., Coonfield, M., *et al.* Notch pathway blockade inhibits glioblastoma growth by depleting CD133 positive stem-like cancer cells. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 5001, AACR 2008, Philadelphia, PA.
 34. Ginestier, C., Charafe-Jauffret, E., Liu, S., *et al.* The IL8/CXCR1 axis regulates breast carcinoma stem cells. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 5004, AACR 2008, Philadelphia, PA.
 35. Rasheed, Z. A., Yang, J., Wang, Q., *et al.* The functional stem cell marker aldehyde dehydrogenase enhances pancreatic cancer stem cell isolation and correlates with clinical prognosis. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 5000, AACR 2008, Philadelphia, PA.
 36. Schwitalla, S., Seidel, J., Keil, S., *et al.* Breast stem cells spontaneously fuse with breast cancer cells: Impacts on cancer stem cell formation. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 5007, AACR 2008, Philadelphia, PA.
 37. Kudo-Saito, C., Shirako, H., Kawakami, Y. Immunosuppressive mechanisms induced by tumor cells during epithelial-mesenchymal transition leading to tumor metastasis. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2465, AACR 2008, Philadelphia, PA.
 38. Wu, J. D., Atteridge, C. L., Wang, X., *et al.* Inhibiting shedding of the NKG2D ligand mic prevents tumor formation by transformed cells. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2466, AACR 2008, Philadelphia, PA.
 39. Badoual, C., Bouchaud, G., Agueznay, N., *et al.* Release of the soluble alpha chain of IL-15 receptor: A new tumor evasion mechanism

- associated with poor clinical outcome in head and neck cancer patients. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2467, AACR 2008, Philadelphia, PA.
40. Ueda, R., Kohanbash, G., Sasaki, K., *et al.* Dicer-regulated micro RNAs 222 and 339 promote immune-escape of cancer cells through downregulation of ICAM-1. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2468, AACR 2008, Philadelphia, PA.
 41. Curtin, J. F., Edwards, M. R., Michelsen, K. S., *et al.* Immune-mediated brain tumor regression requires HMGB1 release and subsequent TLR2 activation on tumor infiltrating dendritic cells. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2469, AACR 2008, Philadelphia, PA.
 42. Frey, B., Pausch, F., Rodel, F., *et al.* Annexin A5 is an important inflammatory modulator of immune responses against apoptotic and necrotic cells and should be accounted as molecular therapeutic for combined cancer therapies. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2470, AACR 2008, Philadelphia, PA.
 43. Novitskiy, S., Ryzhov, S., Zaynagetdinov, R., *et al.* Adenosine and A2B adenosine receptor in regulation of dendritic cell differentiation and properties. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2472, AACR 2008, Philadelphia, PA.
 44. Lin, Y., Michael, G. P., Kent, N. C., *et al.* A population of immunosuppressive CD14⁺ monocytes found in glioblastoma patients inhibit DC differentiation and T-cell function. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2471, AACR 2008, Philadelphia, PA.
 45. Xu, S., Roses, R., Xu, M., *et al.* Induction of IL-12 and IL-23 through toll-like receptors in dendritic cells differentially regulates the balance between chronic inflammation and anti-tumor immunity: implications for cancer vaccines and carcinogenesis. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2473, AACR 2008, Philadelphia, PA.
 46. Kortylewski, M., Xin, H., Kujawski, M., *et al.* Stat3 underlies IL-23-mediated suppression of anti-tumor immunity. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 4199, AACR 2008, Philadelphia, PA.
 47. Teramoto, K., Kitamura, S., Fujita, T., *et al.* Inhibition of hypoxia-inducible factor-1 (HIF-1) in tumor tissue can suppress expression of transforming growth factor-beta (TGF- β) and augment anti-tumor immune responses in tumor-bearing mouse. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2475, AACR 2008, Philadelphia, PA.
 48. Zuo, T., Lin, H., Kuo, C., *et al.* Tumor microenvironment: An integral player in triggering epigenetic silencing in breast epithelial cells. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2533, AACR 2008, Philadelphia, PA.
 49. Yang, L., Huang, J., Ren, X., *et al.* Abrogation of TGF β signaling in mammary carcinomas recruits Gr-1⁺CD11b⁺ myeloid cells that promote metastasis. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 4194, AACR 2008, Philadelphia, PA.
 50. Perentes, J. Y., McKee, T., Ley, C. D., *et al.* *In vivo* imaging of tumor associated fibroblast interaction with collagen fibers reveals a novel mechanism of extracellular matrix remodeling in tumors. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 4204, AACR 2008, Philadelphia, PA.
 51. Weiser-Evans, M., Choudhary, R., Kaplan-Albuquerque, N., *et al.* Deletion of cytosolic PLA2 in the tumor microenvironment inhibits progression and metastasis of lung cancer. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 5793, AACR 2008, Philadelphia, PA.
 52. Ozpolat, B., Akar, U., Chaves-Reyes, A., *et al.* Targeted silencing of bcl-2 alone or combination with chemotherapy induces massive autophagic cell death in bcl-2 overexpressing breast cancer cells. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 4928, AACR 2008, Philadelphia, PA.
 53. Santiskulvong, C., Fekete, M., Eng, C., *et al.* Dual inhibition of phosphoinositide 3-kinase and mammalian target of rapamycin as a novel therapeutic approach in human ovarian carcinoma. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 4970, AACR 2008, Philadelphia, PA.
 54. Sharma, S. V., Lee, D. Y., Way, I. P., *et al.* Cell culture modeling of combination therapy to prevent acquired resistance to EGFR kinase inhibitors in non-small cell lung cancer. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract SY12-04, AACR 2008, Philadelphia, PA.
 55. Kuwai, T., Nakamura, T., Sasaki, T., *et al.* Targeting the EGFR, VEGFR, and PDGFR on colon cancer cells and stromal cells is required for therapy. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2576, AACR 2008, Philadelphia, PA.
 56. Rosano, L., Masi, S., Cianfrocca, R., *et al.* Endothelin A receptor promotes ovarian cancer metastasis: implications for an effective targeted-therapy. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 2574, AACR 2008, Philadelphia, PA.
 57. Cho, W. C. Proteomic approaches to cancer target identification. *Drug Discov Today: Ther Strategies* doi:10.1016/j.ddstr.2008.02.007 (2008).
 58. Wang, A. Z., Gu, F., Zhang, L., *et al.* Development of novel multifunctional nanoparticles for targeted delivery of concurrent chemoradiotherapy. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract 4159, AACR 2008, Philadelphia, PA.
 59. Baron, J. A. Calcium and vitamin D: promising or proven. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract SY33-01, AACR 2008, Philadelphia, PA.
 60. Talalay, P. The chemopreventive power of crucifers: isothiocyanates and glucosinolates. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract SY33-03, AACR 2008, Philadelphia, PA.
 61. Yang, C. S. Dietary polyphenolic compounds in cancer prevention. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract SY33-04, AACR 2008, Philadelphia, PA.
 62. Kim, Y. J. Folate and cancer prevention. In: *American Association for Cancer Research Annual Meeting: Proceedings, 2008 Apr 12-16, San Diego, CA*. Abstract SY33-02, AACR 2008, Philadelphia, PA.
 63. Cho, W. C. A future of cancer prevention and cures: highlights of the Centennial Meeting of the American Association for Cancer Research. *Ann Oncol* 19, 205-211 (2008).

Received: June 19, 2008; Accepted: June 27, 2008

