The Ninth Annual American Association for Cancer Research International Conference on Frontiers in Cancer Prevention Research

Li Xu1, Sophia S. Wang2, Megan A. Healey3, Jessica M. Faupel-Badger4, Jason A. Wilken5, Tracy Battaglia6, Eva Szabo7, Jenny T. Mao8, and Raymond C. Bergan1,9

Abstract
The Ninth Annual AACR Frontiers in Cancer Prevention Research conference was held in Philadelphia in November 7–10, 2010. Its thematic focus was "Prevention: From Basic Science to Public Health Benefit." Telomere plasticity, the microenvironment, inflammation, transformation to the metastatic phenotype, and pathways to obesity were highlighted as important elements of carcinogenesis amenable to intervention. The integration of information from novel technologies related to physical biology, molecular and genetic profiles, and imaging along with behavioral and clinical parameters have advanced risk stratification and early detection. Cancer prevention represents a powerful testing ground for the development of individually tailored intervention and for increasing the efficiency of drug discovery. Advances in clinical trials relate to more efficient design strategies, have shown first-in-human targeting capabilities, and have developed powerful strategies to overcome accrual barriers. Tailored intervention strategies now show high efficacy on large cohorts across several cancer types. These successes are expected to increase.

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length has been linked to aging and cancer. Building on her work that led to a Nobel prize, Elizabeth Blackburn linked the molecular regulation of telomeres to public health considerations. New studies indicate that there is a plasticity to the regulation of telomeres and that this regulation is affected both by genetic and environmental factors. Several studies were cited, ranging from dietary interventions (e.g., omega-3 fatty acids) to individuals with high levels of perceived stress (e.g., caregivers of dementia patients), showing that lifestyle factors are associated with altered telomere length. These findings provide the rational for expanding investigations on the role of telomere plasticity and its modulation for cancer prevention.

The microenvironment was an important area of focus. Historically, it was viewed as a static physical platform on which epithelial cells evolved into cancer. New data point to the microenvironment's active role in carcinogenesis and provide clues for targeted preventive therapies. In pregnancy-associated breast cancer (PABC), recent findings invoke an invasion hypothesis wherein breast tissue remodeling that occurs after birth involves programs typically associated with wound healing. Pepper Schedin described how this involves an influx of immune cells. The associated inflammation alters the integrity of the extracellular matrix, facilitates early steps in carcinogenesis, and enhances metastatic spread. In xenograft models of PABC, the anti-inflammatory drug ibuprofen reduced tumor-associated collagen, tumor size, and metastasis. Postpartum gland involution may therefore present a promising window for prevention of PABC.

New findings identify race-based differences in the microenvironment that may explain in part racial differences in cancer incidence and prognosis. Stefan Ambbs has identified distinct immune signatures associated with inflammations as poor prognostic indicators in both breast and prostate cancers of African Americans. These studies suggest that changes in noncancer cells contribute to carcinogenesis and are race specific. Further, therapeutic targeting of these changes and its efficacy may well be, at least in part, race specific.

Separate investigations underscored the role of DNA damage and telomere malfunction in affecting the microenvironment. In breast epithelial cells, changes in DNA physical makeup are permissive for progression in cells lacking p16. Thea Tsoti showed that cells "activated" in this manner can initiate abnormal changes in normal neighboring breast epithelial cells in a nonautonomous manner, thereby promoting carcinogenesis in neighboring cells.

A primary focus on inflammation's role in carcinogenesis was a prominent theme. The role of neutrophil elastase in tumor progression was described by McGarry Houghton. Elastase released by neutrophils is taken up by adjacent epithelial lung tumor cells, in which it degrades insulin receptor substrate-1. This facilitates phosphoinositide 3-kinase (PI3K) interaction with platelet-derived growth factor receptor, thereby stimulating tumor cell proliferation. Neutrophil elastase was presented as a potentially important chemoprevention target.

Several novel approaches were described that focused on understanding early cancer events and identifying associated chemoprevention targets. By applying a systems biology approach to breast cells from women at high risk for breast cancer, changes in protein network signaling could be identified. Through this approach, 3 signaling pathways were identified whose activation was associated with elevated breast cancer risk: cSrc/PI3K/Akt/mTOR, EGFR/MEK/ERK, and HER2/bcl-2. Drugs that lower the degree of activation of these pathways may lower risk and prevent breast cancer. In a separate approach, gene expression patterns were profiled in phenotypically normal epithelial cells from individuals with germ line mutations that predispose to cancer, including BRCA1, BRCA2, APC, and VHL. Alfonso Bellacosa described changes in the expression of genes with previously established links to cancer, and of other genes that seem to confer a small growth advantage. When coupled to the underlying genetic context, this may confer a large biological impact. He emphasized that phenotypically normal cells harboring mutations linked to cancer provides a powerful platform to study early molecular changes driving carcinogenesis.

The undefined role of androgens in early prostate carcinogenesis was a thematic focus. It was emphasized that androgen levels decline with age, that androgens promote differentiation of prostate epithelial cells and that the role of androgens in early prostate carcinogenesis remains elusive. William Nelson showed that androgen receptor (AR) and topoisomerase II-beta (TOP2B) are corecruited to TMPRSS2-ERG genomic breakpoint sites, triggering DNA double-strand breaks and the formation of de novo TMPRSS2-ERG fusion transcripts. These findings implicate AR/TOP2B in the creation of TMPRSS2-ERG rearrangements, which are present in half of all prostate cancers. Shuk-mei Ho emphasized the role of age-related increases in the estrogen to androgen ratio in prostate carcinogenesis. These findings identify potentially important targets for chemoprevention.

Collectively, new findings and concepts presented at this meeting highlighted the bidirectional nature of research spanning prevention and carcinogenesis and the intimate link between these 2 fields. The powerful synergy between these areas is shown by the spectrum of innovative insights encompassing heretofore unknown basic biology and unimagined preventive strategies.

Risk Stratification and Its Modulation for Cancer Prevention

Efficient cancer prevention strategies are directed by underlying risk. Therefore, cancer prevention represents a focal point that drives us to refine our understanding of risk. Advances in our understanding of carcinogenesis, coupled to novel technology, provides us with a greater knowledge of this critical area. The importance of risk stratification and the use of multiplex-based approaches to more accurately define risk were predominant themes. Integrating these concepts with novel imaging
and biomarker techniques provides new capabilities for early detection.

Inflammation can have protumorigenic or antitumorigenic effects. By comparing the expression pattern of inflammatory-related genes, including micro-RNAs, in tumors and paired noncancerous tissues, an inflammatory gene expression signature was identified that improved predictions for outcome over single biomarkers. Curtis Harris speculated that the resultant inflammatory risk score might be useful in several cancer subtypes for identifying high-risk, early-stage patients to assist in decisions regarding appropriate therapeutic intervention.

Douglas Easton addressed the complexity of breast cancer genetics. The vast majority of familial breast cancers do not arise from mutations of high-risk BRCA1, BRCA2, p53, or PTEN genes. Genome-wide association studies (GWAS) indicate that breast cancer risk is polygenetic. Individual genes contribute a small positive or negative effect, which are cumulative. The heterogeneous nature of breast cancer implies that unique polygenic profiles will likely be seen within a given breast cancer subtype. From this standpoint, GWAS were used to define a 13 single nucleotide polymorphism (SNP) breast cancer signature that could be used to further refine risk estimates in BRCA2 carriers. These studies illustrate the power of combining GWAS-derived biomarkers with existing clinical markers to increase the accuracy of risk stratification.

Several speakers discussed biomarker complexity. Members of the epidermal growth factor receptor (EGFR) family, including EGFR and HER2 subtypes, contribute to carcinogenesis and constitute validated pharmacologic targets. However, determining which patients will respond to treatment is still a challenge. Nita Mahile emphasized that the manner by which biomarkers are measured constitutes an important factor. Serum- and tissue-based assays are not always concordant. Alternative isoforms of a biomarker must also be considered. For example, the truncated and constitutively activated isoform “p95” HER2 is not differentiated from full-length HER2 in most expression assays. Similarly, EGFR is not a predictive marker of responsiveness to cetuximab in colorectal cancer. A reason for this may relate to the expression of alternate EGFR isoforms in tissue and blood. Although full-length EGFR is not proteolytically shed into blood, its soluble form (sEGFR) is proteolytically released, and blood concentrations of sEGFR seem to predict survival.

Other talks highlighted the use of autoantibodies in cancer detection. The importance of using panels of markers to define risk was a prominent theme in these talks. The potential of this approach was highlighted in studies that evaluated prediagnostic sera from the carotene and retinol efficacy trial (CARET) lung cancer prevention study. However, Samir Hanash discussed that autoantibody responses varied over time and that the kinetics of variance differed with each autoantibody. A panel of autoantibodies will thus be required to reach optimal sensitivity and specificity. This theme also held true for mucin-associated autoantibodies and antigens used in the early detection of pancreatic cancer. Michael Hollingsworth therefore recommended that using a panel of markers as small lesions may not produce detectable levels of some markers.

Another approach to risk centered on pairing the concept of field cancerization with state-of-the-art molecular and physical biology–based technology. At present, cancer is diagnosed by cellular changes that are visualized through a microscope. Hemant Roy explained that cancer-associated micro- and nano-architectural changes in the physical nature of cells can be detected with novel technology prior to the development of visually evident changes. For example, using low-coherence enhanced backscattering via a fiberoptic probe to identify cancer-associated changes in the proximal rectal mucosa, 90% of advanced colonic adenomas could be detected. Partial-wave spectroscopy is another promising technology that is able to identify architectural changes in cells from a rectal brushing, with single cell resolution. These technologies have a high potential for risk stratification, and are likely applicable to other organ sites. Their use on buccal swabs can discriminate between smokers with and without lung cancer with excellent performance. This approach provides a promising platform for population prescreening. Ongoing studies are evaluating its predictive potential in the context of prospective intervention with chemoprevention agents.

The newly released positive results of the National Lung Screening Trial, which tested the effect of helical computerized tomography (CT) screening on lung cancer mortality, were highlighted as an important advance on which we can build. An important avenue involves developing biomarkers able to identify those who would most benefit from CT-based screening. By profiling the gene expression of normal appearing airway epithelial cells from smokers with lung cancer versus those with benign conditions, Avrum Spira has identified a predictive gene signature. Current efforts are now seeking to extend this approach to cells obtained from the more readily assessable nasal mucosa. In a related area, Stephen Hecht discussed the potential of polycyclic aromatic hydrocarbons as phenotypic indicators for lung cancer susceptibility in smokers. Stephen Lam presented new information regarding the natural history of bronchial preneoplasias and their potential as markers of cancer risk beyond the proximal bronchi.

Impressive advances in novel technology, along with an integrated consideration of molecular, genetic, physical biology, and clinical parameters, has led to advances in early detection and to our understanding of risk. Ongoing advances will allow us to refine risk at the level of the individual and to use this information to tailor preventive approaches.

**Cancer Prevention Provides a Powerful Testing Ground for Evaluating Behavior and Therapeutic Intervention, and for Drug Discovery**

When cancer is at an early phase of carcinogenesis, the efficacy of intervention is proportionally greater than in the advanced setting. This stems from concepts related to
reversibility of the biological process, fewer aberrant proteins that need to be pharmacologically targeted, and a lower burden of confounding clinical factors. For these very same reasons, cancer prevention provides a unique avenue for drug discovery. The latter relates to the ability to examine the biological consequences in the human system after administration of a nontoxic agent.

Mitogen-activated protein kinase kinase 4 (MKK4; also known as MEK4) has been shown to increase matrix metalloproteinase 2 (MMP-2) and cell invasion in human prostate cancer cells. The potential chemopreventive agent genistein inhibits MKK4 kinase activity in vitro, MMP-2 and cell invasion in vitro, and it prevents human prostate cancer metastasis in animals. In a phase II trial, genistein was shown to decrease MMP-2 expression in human prostate epithelial cells. Using gene expression profiling of prostate epithelial cells from this study, Raymond Bergan showed that genistein selectively modulated genes that regulate cell motility. He highlighted this as a proof-of-principal that genistein selectively modulated genes that regulate cell motility.

Activation of the PI3K pathway in bronchial airway epithelial cells has been linked to dysplasia and lung cancer development in smokers. Andrea Bild discussed how myo-inositol, a potential chemopreventive agent, inhibits PI3K pathway signaling in airway epithelial cells in humans treated with the drug. These findings suggest that inhibition of PI3K pathway activation is an important pharmacologic target and that further studies of myo-inositol for lung cancer prevention are warranted.

Epidemiologic studies link the use of antidiabetic agents, pioglitazone and rosiglitazone (both PPAR-γ agonists), and metformin (an inhibitor of insulin/IGF receptor signaling) to lower risk of several cancers, including lung and head and neck. Eva Szabo discussed the inhibition of carcinogenesis by PPAR-γ agonists in preclinical in vitro and in vivo models, and described high efficacy in a phase II trial for treatment of oral leukoplasia. Michael Pollak discussed the importance of the insulin/IGF-1 receptor signaling pathway for cancer prevention, and further highlighted the potential pharmacologic and economic advantages of using metformin to do so.

Obesity and cancer risk was an important topic. Speakers highlighted obesity as a target for behavioral and therapeutic intervention. African American and Hispanic populations are more prone to obesity, are considered high susceptibility populations, and may require specialized intervention strategies. Findings from the Women’s Health Initiative study, the Nurses Health Study, and the Iowa Women’s Study cohorts all associate decreased weight with decreased breast cancer risk. Anne McTiernan noted, however, that the associated beneficial effects of physical activity were greatest among normal weight women, whereas obese women were afforded a lesser beneficial effect. Further, high estradiol was associated with both low physical activity and obesity. Finally, the Nutrition and Exercise in Women study revealed that diet in particular led to significant decreases in the levels of estrogen and inflammatory markers.

Additional speakers highlighted pathways linked to obesity and energy generation, their potential as chemoprevention targets, and their therapeutic targeting. NF-E2–related factor 2 (Nrf-2) is a transcription factor whose age-related decrease in expression is attenuated by caloric restriction. Using mouse models, Rafael de Cabo showed that caloric restriction reduced oxidative stress, delayed onset of tumor genesis, and decreased tumor burden, and showed that these effects were dependent on Nrf2. Other investigations focused on hexokinase 2 (HK2), which converts glucose (G) to G-6-phosphate. HK2 is inhibited by 3-bromopyruvate (3BP) and Peter Pedersen described how 3BP inhibited tumor growth in several animal models. The mTOR pathway was discussed as an important target. Its inhibition can decrease obesity and increase insulin sensitivity in mice. George Thomas described how metformin and 2-deoxy-2-glucose, both of which lead to mTORc1 inhibition, have efficacy in animal models. These studies support the notion that targeted inhibition of energy generating pathways may be an important means of cancer chemoprevention.

New findings presented at the meeting describe novel and important advances that closely link ties between intervention, biological targets, and prevention. Chemoprevention trials provide a near-ideal approximation between targeted therapy and its affect on the targeted organ system. They also offer a novel platform for early steps in the drug discovery efforts.

Tailoring Therapy to Individual Molecular Profiles

Different routes of carcinogenesis can lead to the development of a single type of cancer. A unified theme at the meeting was that the delivery of optimally targeted therapy will therefore require treatment tailored to each individual’s cancer.

Several examples of novel approaches designed to examine tailored therapy were presented by Scott Lippman. A head and neck cancer risk prediction model combined behavioral characteristics and medical history with genetic variations associated with risk. With the Erlotinib Prevention of Oral Cancer study, the EGFR expression level and gene copy number in association with premalignant lesions are taken into consideration. In the Biomarker-integrated Approaches of Targeted Therapy of Lung Cancer Elimination program, a tumor biomarker analysis was used to assign subjects with advanced non–small cell lung carcinoma to 1 of 4 phase II studies.

Analysis of clinical samples collected during the recently completed selenium and vitamin E cancer prevention trial (SELECT) prostate cancer prevention trial is now shedding
light on selenium biology and prostate cancer. Men with low baseline levels of selenium seemed to benefit from selenium treatment, whereas men with high levels did not. Jing Ma further relayed that SNP-based genotyping of the selenoprotein, SEP15, identified polymorphisms associated with high prostate cancer mortality, and polymorphisms which seem to affect selenium efficacy.

Separate studies focused on colon cancer. The ornithine decarboxylase (ODC) SNP, ODC 316A, was found to associate with reduced risk of adenoma in those patients taking aspirin. Eugene Gerner showed that individuals with lower dietary polyamines had the greatest benefit from difluoromethylornithine (DFMO) plus sulindac in a phase III placebo controlled colorectal adenoma prevention trial.

Other studies focused on the genetic context of tobacco cessation. CYP2A6 is responsible for 90% of nicotine metabolism, and CYP2A6 polymorphisms affect the rate of nicotine metabolism. Slower metabolizers have a higher quit rate with the nicotine patch. Robert Schnoll highlighted that CYP2A6 is a genetically informed biomarker for assigning patients to different therapeutic approaches.

Collectively, these findings highlight the importance of developing a thorough understanding of the following trial: (i) the underlying differential molecular profiles that can drive carcinogenesis for the same cancer, (ii) the molecular pharmacodynamics of the chemopreventive agents, and (iii) the pharmacokinetics of those agents.

Important Early-Phase Clinical Trial Findings

Several recently completed early-phase chemoprevention clinical trials, highlighting important new findings were presented.

Phase 0 trials enable go/no-go decisions to be made on relevant human models. This is advantageous because animal data have poor predictive value for performance in humans. To accelerate the clinical development of an orally active AKT pathway inhibitor, SR13668, Joel Reid conducted the first-ever phase 0 chemoprevention trial to compare the effect of 5 different formulations on bioavailability. They rapidly identified a lead formulation for further clinical testing. These findings support application of the phase 0 trial paradigm to accelerate chemoprevention agent development.

In preclinical models, genistein inhibits the initial conversion of human prostate cells to a metastatic phenotype. In the first-ever chemoprevention trial designed to prevent conversion of cells to a metastatic phenotype, Raymond Bergan conducted a phase II trial of genistein in subjects with localized prostate cancer. Analysis of genistein’s effects on tissue, and prostate epithelial cells in particular, showed that it decreased MMP-2 expression, selectively modulated genes that regulate cell motility, and induced nuclear morphometric changes in cells consistent with inhibition of cell detachment. Changes in each of these sets of biomarkers denote efficacious action on initial steps in metastatic transformation. These findings show that it is possible to therapeutically revert the metastatic phenotype in humans.

Bowman–Birk inhibitor concentrate (BBIC) inhibits chymotrypsin protease activity in preclinical models. Frank Meykens performed a double-blind randomized placebo-controlled phase II trial by using BBIC in 148 subjects with oral leukoplasia. Even though the outcome was negative, the study was powered to provide a definitive assessment of BBIC efficacy, and thus provided important scientific information at an early stage.

Joanne Jeter conducted a phase II study to evaluate the safety and efficacy of topical DFMO and topical diclofenac in the treatment of sun-damaged skin. The study indicated that it is feasible to use nuclear karyometric values as an endpoint. Furthermore, combinational therapy is superior to single-agent treatment.

These studies highlight the roadmaps for more efficient clinical trial designs and practices, and they describe novel therapeutic advances. They open up exciting new avenues which should be pursued through future investigations at the basic and clinical levels.

The Power of Prevention

With cancer prevention, intervention takes place early in the process of pathogenesis. As such, there are fewer molecular abnormalities requiring correction, the abnormalities are relatively better defined and can be more readily targeted, and the consequences of targeting them have proportionally greater efficacy. These conditions are best epitomized in the case of breast cancer. In the metastatic setting, multitarget cytotoxic therapy has only a temporizing effect on disease outcome. In contrast, targeted therapeutic intervention with a relatively nontoxic single agent in a cohort at risk for breast cancer cuts the chance of ever developing cancer in half. These basic considerations hold true for all cancers, and taken in the context of current successes in the field, they underscore the power of cancer prevention.

In colon cancer, a 20-year follow-up trial indicates that aspirin reduces cancer risk by 55%. From his study of DFMO and sulindac, Eugene Gerner relayed that treatment reduced adenomas by 70% and advanced adenomas by 90%. This highlights the power of drug combinations, taking advantage of drug synergy to increase efficacy and reduce toxicity.

Liver cancer is a major cause of cancer death worldwide. Aflatoxin exposure from the food supply further increases risk in people infected with hepatitis B virus (HBV). After defining the epidemiology of aflatoxin exposure and HBV infection across regions in China, John Groopman used chlorophyllin to modulate aflatoxin pathways in high-risk cohorts and is seeing a 55% reduction of DNA damage. His translational research efforts are impacting high-risk populations throughout the world. For this work he was awarded the Ninth Annual AACR-Prevent Cancer Foundation Award for Excellence in Cancer Prevention Research.

Infectious agents cause 1 in 6 cancers worldwide. Human papilloma virus (HPV) causes cervical cancer. Current vaccines are effective in decreasing HPV infection, are in
widespread use and Douglas Lowy conveyed that longitudinal studies are expected to show a reduction in cervical cancer. HBV causes liver cancer. Mei-Hwei Chang reported that by vaccinating children in Taiwan against HBV on the basis of liver cancer incidence, they are already seeing a 70% reduction in childhood liver cancer. With aging, proportionally higher improvements are expected.

Clinical trials represent a critical aspect of the research enterprise. However, their conduct, and in particular the ability to accrue subjects, constitutes a major intractable roadblock to advancing research. The power of dedicated organization is manifest in the Susan Love Foundation’s Army of Women program. Leah Wilcox conveyed that more than 343,000 women have been recruited into the "Army." Of the 38 studies that have launched within the Army, most reached their target sample sizes within a week. This group has effectively forged a path through a critical roadblock, and in so doing they have created a new paradigm for the broader research community.

As we advance forward, it is critical to realize that poverty is the cause of disparate health outcomes, and this factor transcends geographic location, race, and ethnicity. In talks by Electra Paskett, Roshan Bastani, Tracy Battaglia, and Jane Wardle, examples were presented that encompassed various countries, populations, and cancer types. The consensus was that unique community-specific solutions will need to be developed for each specific type of intervention.

Our public health officials are on the front line of implementing prevention strategies. The strength of the research supporting the rational for delivery to the public is a prime determinant of their ability to successfully implement effective strategies. Efficacy is now being seen on a global level. Through a coordinated combination of marketing restrictions, aggressive warning labels, increased taxes, and smoking bans, Michael Thun relates that smoking rates in Thailand have been reduced. Through a similar multipronged approach, Thomas Farley reports significant success in reducing smoking rates in New York City. Learning from India’s ability to reduce oral cancer mortality by 34% through a comprehensive oral leukoplakia screening program, Miriam Rosin reports the rollout of a Canadian program on the basis of this success. Australia has one of world’s highest rates of skin cancer. Craig Sinclair reports that media campaigns about the dangers of sunburn are now having an impact on younger age groups, in which skin cancer rates are declining.

From basic concepts of carcinogenesis and targeted intervention one can inextricably conclude that major advances in the war on cancer will be made through prevention-based approaches. The accomplishments presented at this meeting provide factual evidence in support of this statement. Years of basic and preclinical research have now been translated into major tangible advances in public health. Even more impressive is that with our advancing understanding of carcinogenesis and targeted intervention, these success stories will only increase in number and in breadth. As we progress forward, it is imperative for us to find ways to ensure that all populations are able to reap the benefits.

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