

Foreword

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The six manuscripts in this special issue of *Cancer Biomarkers* summarize key discussions at the Haifa Prevention Workshop. The workshop, held at the Dan Carmel Hotel in Haifa, Israel from May 4 to May 6, 2004, is an intensive three day meeting that addresses important questions and controversies in translational cancer prevention.

Risk Identification

The issues of environmental exposures and life style were examined by Drs. Leslie Bernstein, Margaret Spitz, Frank Meyskens, Steven Lipkin, Gad Rennert, Paolo Buffeta, Zvi Livneh and Stephen Gruber.

Dr. Bernstein pointed to sufficient data to link colorectal cancer, breast cancer, endometrial cancer, ovarian cancer with exercise and activity. In some of these models, there appears (for example, endometrial cancer) to be a linear relationship with quantity of physical activity and risk of transformation. For colon cancer, job activity correlates with risk of transformation. However, the methodological tools remain problematic. The facets of activity, the time periods, interview reliability of many of the instruments remain problematic. Nevertheless, the link between physical activity and carcinogenesis risk is important and should be developed further through improved data collection instruments.

Dr. Spitz described the increasing linkage between tobacco smoke exposure and genetic function. For example, concordance rates of smoking and nicotine addiction are higher among twins than within non-twin families. There is increasing evidence that risk of sustained nicotine dependence is linked to genetic polymorphisms in neurotransmitter systems such as the dopamine pathway, in nicotinic acid receptor structure and function, in metabolic genes (for example, CYP 2A6), and in DNA repair system genes. The current

barriers to widespread phenotyping include concerns regarding the specificity of genetic polymorphism functional impact, assay cost and usefulness, incomplete risk assessment models, and weaknesses in biomarker surrogates being used for target tissue endpoint disease.

In the case of melanocyte carcinogenesis, Dr. Meyskens suggested that heavy metal exposure with enhanced oxidation of reactive oxygen species may play a crucial role. Environmental and occupational exposures to redox active metals such as copper, iron, manganese, and lead may enhance carcinogenesis in melanocytes. Chelating agents, environmental modification may be a critical approach to reduction of melanoma.

In the case of colonic carcinogenesis, Dr. Gruber describes in the paper in this issue [1] the large molecular epidemiology study of the I1307K gene missense substitution resulting in a hypermutable tract gives a somatic mutational fingerprint. This haplotype may amplify environmental stress associated with colonic carcinogenesis. For example, in I1307K carriers, vegetable consumption caused at 50% risk reduction in cancer incidence. Physical activity (sports activity) and aspirin or NSAID intake also reduced colon cancer risk.

In a paper published in this issue [2], Dr. Livneh described a new paradigm to risk assessment is being developed through the use of functional assays of critical cellular components that ensure the fidelity of key control systems. DNA repair may be one of these systems. In the case of DNA repair, the cell has multiple pathways to ensure DNA fidelity, some pathways of high quality but with high energy and protein expenditure and others of lower quality but minimal energy expenditure. Polymorphisms in key components of the DNA repair system may impair functionality of these pathways, leading to loss of DNA fidelity in situations of

stress. The OGG1 functional assay is one of potentially multiple approaches to interrogate the DNA repair system clinically and provide critical risk assessment information for tumors associated with environmental exposures such as tobacco smoke, lipid peroxidation, and other oxidative stress mechanisms.

The recognition that genetic haplotypes which result in hypermutable genetic segments amplify environmental risk of transformation is a powerful concept that warrants intensive future scientific investigation. Risk assessment in the future is likely to lie with the ability to assess gene environmental interactions functionally. Genetic risk will be based upon haplotype based polymorphic variations that are functionally important. While assessment of genetic risk may be quantified genetically, high throughput, inexpensive functional assays of genetic polymorphisms may be preferable.

Screening and Early Detection

Issues in screening and early detection were addressed by Drs. Sudhir Srivastava, David Ransohoff, Laurence Freedman, Ari Admon, and Robert Bresalier.

Biomarkers should be developed using new high throughput technologies for serious, life threatening illness. Ultimately, biomarkers need some biological plausibility, although one might argue that the products being discovered using high throughput technologies will overwhelm the scientific community's ability to recognize mechanistic linkages. The many barriers to validating biomarkers for the diagnosis or risk assessment of malignant neoplasms have reduced productivity in this field. Among these barriers lead time bias, biosample bias, the gold standards for validation, generalizability, and partially informative markers need to be dealt with systematically for any future success. Among the tools available to minimize the multiple sources of bias are high quality sample ascertainment and storage, training set and test set validation designs, and rigid statistical analysis of variability in both the assay technique and in the diagnostic outcome. Developing and applying these tools requires substantial investment in analytical resources, informatics and biosample repositories, collaborative environments, and skilled personnel.

Dr. Freedman reviewed the statistical issues surrounding the design and analysis of surrogate outcomes [3]. He noted that the aim of interventions is usually to prevent the development of a specific cancer. The most naturally relevant outcome is the occurrence or not of the cancer within a defined long-term time frame; but, long time frames are not feasible with limited resources. Dr. Freedman outlined the different

types of biomarkers surrogates that can be used in place of a cancer occurrence endpoint and suggested that the Prentice model commonly used to determine the dependence of a surrogate upon a specified outcome may not hold for a phase III outcome. Rather, Prentice models should be retained as endpoints in phase II research.

Specific examples of the different approaches to biomarker discovery and validation were addressed by Dr. Srivastava. As described in the paper published in this issue [4], Dr. Admon described the current state of the art and potential future of proteomics. Holding great future promise, high throughput proteomics analytics are migrating to a new generation of equipment that will provide better dynamic range and individual protein specificity. The first generation, represented by SELDI, has made important contributions to the concept of high throughput proteome interrogation. Whether this technology will be sufficiently reproducible for clinical applications remains an important research question.

Another example of biomarker development, a mucin glycoprotein product for early detection of colonic malignancy, demonstrates the development of a biomarker through the classical route of mechanism based research identifying a critical product with a role in the carcinogenesis process. This process, while complex and long, results in a discrete product that can be identified using standard analytical methodologies.

Ultimately, success in biomarker based screening and early detection will be based upon the scientific community's ability to integrate diverse analytical tools while maintaining rigorous translational validation in collaborative settings.

Therapeutics

Issues in preventive therapeutics were addressed by Drs. Raju Mehta, Leslie Ford, Nadir Arber, Bernard Levin, Karen Johnson, Powel Brown, Jack Cuzick, Reuben Lotan and Jaak Janssens.

Rodent models remain a crucial preclinical testing tool. Dr. Mehta pointed out that models are developed to describe initiation and promotion schemes. Rodent chemical carcinogenesis models are organ specific and, although not as mechanistically driven as genetically modified models (transgenics, knockouts), remain the mainstay of preclinical efficacy testing because of the ability to model initiation and promotional events. Transgenic models are becoming organ specific and molecular carcinogenesis mechanism targeted. In the future, conditional transgenic models that enable targeted gene and organ site transformation will be important efficacy and biomarker testing models. Chemical carcinogenesis rodent models will remain important in

modeling preventive therapeutic efficacy and biomarker responses.

In humans, the movement of preventive therapeutic agents from broad mechanism, such as antioxidant, to targeted agents will continue. Dr. Arber, in his paper published in this issue [5] suggests that cyclooxygenase-2 inhibitors remain important models of targeted agents although recent data suggests that potent targeting of key carcinogenesis associated pathways may have unacceptable toxicity profiles for healthy populations.

Dr. Lipkin notes in his paper published in this issue [6], that existence of multiple regulatory pathway molecules may limit the effectiveness of single targeted agents. Combining targeted agents requires recognition of the complexity of molecular regulation. A “three dimensional” rather than a two dimensional model of activation and inhibitory molecules exists. Targeted therapies may be useful in limited subjects with specific genetic or environmental stresses that have caused deregulation of critical proliferative, apoptotic, and angiogenic regulatory pathways.

The value of large cancer endpoint trials provoked intensive discussion. One advantage of mounting and completing these extensive, expensive trials in addition to identifying efficacy with a cancer endpoint, is the use of these samples on cohorts to ask other important questions. For example, the large tamoxifen-breast cancer prevention trial has enabled the recognition of tamoxifen’s usefulness in BRCA populations, has enabled probing of signal transduction pathways and response to treatment, and has pointed out the need for recognition of dose response clinical pharmacology data.

The development and validation of dietary interventions as opposed to pharmaceutically based interventions was particularly controversial. Diet modulation is the least toxic or expensive preventive intervention available, yet definitive dietary interventions have not prospectively demonstrated efficacy in preventing common cancers. Instruments to quantify diet reproducibly and accurately remain weak. Adherence to diet modulation regimens requires intensive support by professional personnel. Without prohibitively costly professional support, the effectiveness of dietary modulation for cancer preventive efficacy may be limited.

References

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