

Chemotherapy Foundation Symposium

Epigenetics & Tumor Profiling Can Lead to Clinical Results

By Mark Fuerst

NEW YORK CITY—Advances in epigenetic therapy and tumor molecular profiling are moving the basic science of cancer into meaningful clinical results, according to the participants in a session called “The 21st Century Cancer Revolution” presented here at the Chemotherapy Foundation Symposium.

Session Chairman Samuel Waxman, MD, Clinical Professor of Medicine, Hematology/Oncology, and Oncological Services at Mount Sinai School of Medicine, opened the session by saying, “The way we treat cancer in this century is different from the last century. We have new ways to look at cancer and to dissect it further that were not available before.”

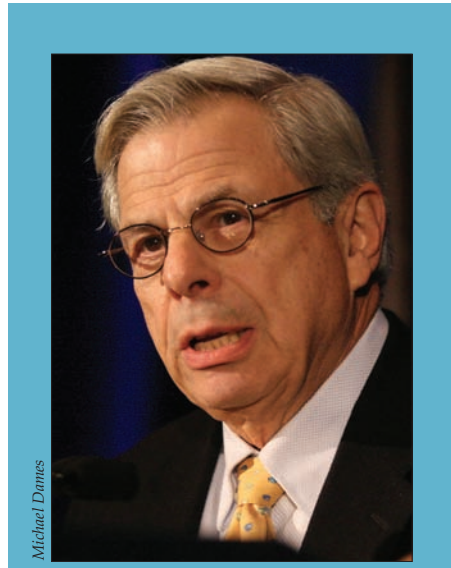
For example, Dr. Waxman said that with the new human papillomavirus vaccine, it should be possible to prevent cervical cancer. Therapies aimed at inducing cancer dormancy or completely eradicating dormant tumor cells may result in new strategies that might improve cancer treatment. And the ultimate goal, personalized therapy, will be available in the near future, he predicted.

“As we better understand how mechanisms, including how normal cells become malignant, are related to various pathways, we can better understand ways to inhibit or stimulate pathways and be able to control the treatment of malignant pathways to normalize them.”

APL

One paradigm of a 21st century treatment that targets abnormal epigenetics is the induction of differentiation that results in a near cure of acute promyelocytic leukemia (APL), said Dr. Waxman, well known for his successful APL research.

“Cancer is associated with abnormal gene expressions often due to defects in non-DNA components, such



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as proteins that modulate gene expression that can be targeted by drugs already approved and in clinical use. The abnormal epigenetic components can be identified by technologies similar to following gene expressions that are already in use in the prediction of therapeutic selection in several forms of cancer,” he said.

In APL, an abnormal transcriptase factor attaches to a complex of proteins. Arsenic overcomes the resistance to all-trans-retinoic acid (ATRA) and “is the single best therapy for treating APL,” Dr. Waxman said.

“Arsenic and ATRA induce apoptosis. They are synergistic by a number of mechanisms, and lead to differentiation and apoptosis without being toxic to the patient. They are more effective in inducing transcriptase together than either agent alone.”

New data from Shanghai researchers, funded by the Samuel Waxman Cancer Research Foundation, show that use of arsenic and ATRA following chemotherapy lead to an event-free survival rate of 95% at five years for APL.

“APL is a great adventure in taking science to the clinic. It’s the first disease, in cancer, that we can say is almost cured,” Dr. Waxman said.

Asked for his opinion after the symposium, Edward Ambinder, MD, the symposium’s Program Director and Associate Chairman, agreed, saying, “As we better understand how mechanisms, including how normal cells become malignant, are related to various pathways, we can better understand ways to inhibit or stimulate pathways and be able to control the treatment of

malignant pathways to normalize them.”

APL is the first model of “how we can utilize simple translocation and transformative treatment of diseases and cure patients,” said Dr. Ambinder, who is Clinical Professor, Medicine/Hematology and Medical Oncology at Mount Sinai School of Medicine. “It’s an indication that this type of research has a chance to cure disease. Translocation occurs in many types of leukemias. Once we are able to find how to reverse translocation, we will see cures of other leukemias as well.”

First-Generation Epigenetic Therapy

First-generation epigenetic treatments are drugs designed to increase acetylation and decrease methylation of histones and gene promoters and express silenced tumor-suppressor genes. “These epigenetic treatments demonstrate clinical efficacy in various hematologic malignancies,” he said.

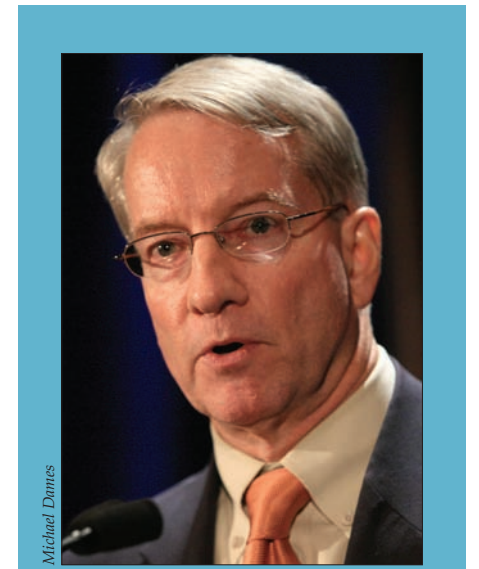
“Clinical trials have demonstrated the safety of combining these drugs, which are generally mildly toxic, with chemotherapeutic agents. New and more specific drugs to modulate gene expression based on targeting specific enzymes involved in this process demonstrate more efficient pharmacokinetics, bioavailability, and specificity.”

Small compounds designed to inhibit protein-protein interactions induce specific cancer cell death as demonstrated by the targeted inhibition



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of Bcl-6, the significant molecular aberration associated with diffuse large B-cell lymphoma. “Epigenetic therapies can correct multiple gene abnormalities whether due to translocation, mutation, or silencing of genes due to abnormal non-DNA components,” he said.



John Wright, MD, PhD: “We need to have more from genomic and proteomic strategies to select the patients who are most likely to benefit from therapy. We need to use combinations of therapies to act against coactivated pathways in aggressive tumors.”

Epigenomics

Another speaker at the session, Ari Melnick, MD, Assistant Professor in the Department of Developmental & Molecular Biology in the Department of Medicine (Oncology) at Albert Einstein College of Medicine, in Bronx, NY, noted that tumor molecular heterogeneity represents a major barrier to effective and specific cancer therapy for individual patients.

“Much of this molecular heterogeneity is encoded by combinations of genetic mutations and epigenetic modifications of the genome. Epigenetic modifications consist in large part of covalent modifications of DNA or its associated proteins, which control gene expression and which can be transmitted and sustained as cells divide.”

Epigenetic marks mediate tumor phenotype and play a critical role in virtually all cancer types during both tumor initiation and progression, Dr. Melnick explained, adding that the study of epigenetic modifications genome-wide is referred to as epigenomics.

Recent advances in microarrays, nucleic acid mass spectrometry, mass-sequencing, and computational biology

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Colorectal Cancer Screening Still Essential for the Elderly

As people get older, their risk of developing polyps and colorectal cancer increases. Currently, there is no clear evidence or established guideline for the upper age limit for colorectal cancer screening by colonoscopy. Two new studies presented at the American College of Gastroenterology's Annual Scientific Meeting suggest the importance of continued colorectal cancer screening among healthy elderly Americans.

One study, led by Matthew M. Baichi, MD, of the University of Buffalo and the VA Western New York analyzed the results of 587 colonoscopies performed there in 2004. Fifty-six patients were age 80 or older and 531 patients were 70 to 79. Data were collected on the number and location of adenomas, histology, presence of advanced adenomas, and colon cancer.

Colorectal adenomas were detected more frequently in older patients. Adenomas were found in about 36% of patients 80 or older and about 20% of those younger than 80. There was a trend for more proximal advanced adenomas in patients over 80 (12.5%) compared with the younger age group (6%).

After a two and a half year follow-up, 72% of patients over 80 were alive compared with 82% of patients between 70 and 79.

"While screening colonoscopy is controversial in patients over 80, age alone should not be a contraindication to colorectal cancer screening," Dr. Baichi said in a news release. "The results of this study suggest that screening colonoscopy should be considered in healthy elderly patients."

In the other study, conducted at Scripps Clinic, Emily G. Singh, MD,


Catherine T. Frenette, MD, and William B. Strum, MD, found that screening colonoscopy extends survival in elderly patients. The question was whether screening colonoscopy led to an earlier stage of diagnosis, thus increasing survival in older patients.

The Scripps analysis included 243 symptomatic and 113 asymptomatic patients diagnosed with colorectal cancer between January 2000 and December 2005. Patient records were obtained from the Scripps Green Hospital Cancer Registry. Patients were divided into two groups based on symptoms and by age and stage of disease at diagnosis.

The stages of colon cancer were separated at a critical point: early stage (Stage 0-IIIB) and late stage (Stage III-IV). A total of 101 patients had Stage I colon cancer, 105 had Stage II, 72 had Stage III, and 61 had Stage IV. The survival rates

of all patients were evaluated from the time of initial colon cancer diagnosis.

After two and a half years of follow-up, asymptomatic patients were found to have significantly increased survival compared with symptomatic patients. There was a sustained difference in stage of disease favoring patients who were asymptomatic, for all ages between 50 and 84, suggesting a role for preventive screening even among those of advancing age.

"We conclude that there is a role for screening colonoscopy in asymptomatic individuals without significant comorbidities up to age 84," Dr. Singh said in a news release, noting that neither the American College of Gastroenterology nor any other guideline groups currently set an upper age limit for colorectal cancer screening by colonoscopy. 

'Epigenomics'

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have made it possible to decode the different levels of the human epigenome from an individual patient's samples, said Dr. Melnick, who also receives funding from the Waxman foundation.

"Our studies using such platforms in leukemia patients demonstrate their greater depth of characterization of biological phenotype and superior clinical prognostication. Along with other recent advances in micro-RNAs and high throughput flow cytometry for cell-signaling pathways, it appears that we are nearing the time when a comprehensive diagnosis of tumor biology could be generated on an individual basis."

Epigenetic therapy drugs are FDA-approved for the treatment of myelodysplasia (for DNA methylation inhibitors) and cutaneous T-cell lymphoma (for histone deacetylase inhibitors). These agents are also in clinical trials both as single agents and in combination for a number of different tumor types. Although epigenetic de-regulation occurs widely, not all tumors are sensitive to these agents.

"In recent work, we have found that human cancer cell lines resistant to methylation inhibitors display a different DNA methylation profile than cells that are sensitive to these agents," Dr. Melnick said. "If such data can be reproduced in the clinical arena, it may become possible to assign to epigenetic therapy only those patients likely to respond, and to avoid ineffective treatment in those resistant tumors."

Additional epigenetic drugs are under development that will target many additional histone modifying enzymes, he said.

"Advances in integrative epigenomic analysis and epigenetic therapy may soon allow design of personalized clinical trials incorporating individual epigenomic profiles and geared toward specific reprogramming of tumor cells," Dr. Melnick said. "The challenge in the next 20 years is to recognize differences between patients and to individualize therapy. Each individual patient has a different phenotype."

One tool useful to identify clusters of tumors is an expression microarray. Gene-expression profiling asks a computer to distinguish in cohorts, which provides a snapshot of the total level of mRNA in a gene at any one time.

"We can see how genes are regulated and their response to stimuli or therapeutic agents," he said. "Small changes can be significant for cancer cells. In addition, with epigenetic regulation we can create a total model of how a tumor cell is distinct in each patient," said Dr. Melnick.

Epigenetic studies can have clinical implications, he said. In examining the genes of acute myelogenous leukemia and acute lymphoblastic leukemia (ALL) patients enrolled in an Eastern Cooperative Oncology Group trial, Dr. Melnick has developed a series of technologies to capture hundreds of involved genes. "Gene networks have patterns that don't coalesce through one biological mechanism. We hope to define a therapeutic target more accurately in the future," he said.

Researchers at Erasmus University have used gene-expression profiling to find a diverse group of gene clusters in leukemia patients, Dr. Melnick noted, explaining that they have associated methylation arrays with gene mutations.


"Some patients with genes that have mutated expressed C/EBP

[CCAAT enhancer-binding protein] alpha transcriptase. Others had high expression of certain T-cell markers. Methylation identified two cohorts—one a T-cell pathway that is expressed, but is not T-cell ALL. Those with methylated genes did poorly, with less than one-year overall survival, while those who did not have methylated genes had more than a three-year overall survival."

'Drug-Development Crisis'

Another speaker, John Wright, MD,

PhD, Senior Clinical Investigator in the NCI's Investigational Drug Branch, said, "We need to have more from genomic and proteomic strategies to select the patients who are most likely to benefit from therapy. We need to use combinations of therapies to act against coactivated pathways in aggressive tumors."

"We are in a drug-development crisis," he added. "The development of drugs has not kept pace with insights gleaned from basis research in cancer. We need new strategies for investigational agents 

RT More Effective than Surgery at Preventing Second Laryngeal Cancers

A study presented at the ASTRO Annual Meeting by researchers from Loyola University Medical Center found that radiation therapy was more effective than surgery in preventing second larynx cancers in patients initially treated for an early larynx cancer.

The study, which lead researcher Gopal Sachdeva, MD, and his colleagues called the largest and only of its kind, included 3,898 patients identified from the NCI's Statistics, Epidemiology, and End Results data base between 1988 and 2003 with histologically proven T1N0M0 Squamous Cell Carcinoma of the Glottic Larynx who underwent Primary Surgery or Primary Radiotherapy.

The long-term cure rates were equivalent with both options, and there was no increased risk of sec-

ond cancers among patients who received radiation compared with the surgical control group, reported Dr. Sachdeva, a resident in radiation oncology. "More importantly, surgical management of these patients resulted in a long-term statistically significant increased risk of developing a second laryngeal cancer, which radiation appears to protect against."

He attributed this to the concept of "field cancerization"—"Whatever the etiological factor, cigarette smoking or alcohol, genetic changes can occur in different areas of the aerodigestive resulting in precancerous and cancerous changes, and in the case of larynx cancer, radiation treats a larger area, essentially the entire voice box. Surgery however usually just addresses the site of the tumor," he explained in a news release.