Meeting Report

In the Forefront of Basic and Translational Cancer Research: Seventh Joint Conference of the American Association for Cancer Research and the Japanese Cancer Association

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Introduction

The Seventh Joint Conference of the American Association of Cancer Research and the Japanese Cancer Association, “In the Forefront of Basic and Translational Cancer Research,” held in Waikoloa, HI, on January 21 to 25, 2007, was designed to showcase the latest advances in all major areas of cancer research and show their translation for clinical benefit. Major advances in technology, paired with significant biological insights, have dramatically accelerated the pace of translational research in recent years. This meeting report describes the highlights of the meeting, stressing technological advances in genomics, proteomics, genetics, and epigenetics; new insights into oncogenic pathways, DNA repair, stem cells, metabolism, and the tumor microenvironment; advances in animal and quantitative models of cancer; novel approaches to cancer prevention and therapy; and progress in individualizing cancer treatment. The conference was remarkably international, and participants gained a global perspective on the cutting edges of cancer research. [Cancer Res 2007;67(10):4556–9]

Advances and Applications of Genomic and Proteomic Technologies

It well known that somatic mutations occur in cancer, leading to altered protein function. Countless genetic mutations occur in cancer, but it is key to determine which of these mutations are critical for cancer progression (“driver”) and which mutations do not contribute to cancer progression (“passenger”). A strategy to distinguish between these driver and passenger mutations was addressed by keynote speaker Michael Stratton (Cambridge, United Kingdom). After sequencing more than 500 protein kinases in more than 200 diverse cancers, he was able to show that driver mutations arise in the cells in a nonrandom manner and lead to a growth advantage. Passenger mutations, although detected in higher numbers, were found randomly throughout the genome and offered no growth advantage. TTN, a large gene encoding a kinase best known for a role in muscle contraction, was identified as having a high probability of having driver mutations and may be involved in cancer through a function in chromosome segregation.

Although Stratton focused on gain-of-function mutations in cancer, Roderick Beijersbergen (Amsterdam, the Netherlands) used a shRNA approach to look at genes in which loss influenced cancer progression. He used a high-throughput screen targeting 8,000 human genes or 14,000 mouse genes, where each shRNA contained gene-specific sequences that act as unique tags, or barcodes, for PCR recovery of shRNA in infected cells. Cells infected with this shRNA library were analyzed for a variety of cellular behaviors, including proliferation, migration, and metastasis. Using this approach, 53BP1 was identified as an essential component of cytotoxicity mediated by Nutlin-3, a chemotherapeutic reagent targeting p53/MDM2 interactions.

Johji Inazawa (Tokyo, Japan) extensively explored genomic aberrations in various types of cancer using in-house bacterial artificial chromosome arrays and identified target genes within novel amplifications or homozygous deletions. Among them, DUSP26, a mitogen-activated protein kinase phosphatase, was identified as the target for 8p12 amplification in anaplastic thyroid carcinoma, one of the most virulent human cancers. Combined with biological studies of DUSP26 function, these results suggest that DUSP26 may be a useful diagnostic marker and therapeutic target for this disease.

Early detection of cancer represents one of the most promising applications of technology to decrease cancer morbidity. In the search for an early biomarker of lung cancer, Yataro Daigo (Tokyo, Japan) investigated genes up-regulated in lung cancer compared with normal lung using microarray RNA profiling. He validated candidates by correlation with clinicopathologic significance and demonstrating an effect on cell growth or invasion when knocked down using RNAi. Genes in which protein products could be detected in sera using ELISA were selected for further evaluation. One such gene, DKK1 (Dickkopf-1, a regulator of the Wnt signaling pathway), was shown to increase tumor invasion, and increased amounts of DKK1 were found in the sera of both lung and esophageal cancer patients. He showed that a combination of high-throughput screening with analysis of candidate genes is an effective approach to identifying potential biomarkers.

Samir Hanash (Seattle, WA) described innovative proteomic approaches to identify biomarkers expressed in preclinical stages of cancer. To facilitate this, he and his collaborators used blood collected from a population of patients at high risk for developing colon cancer and, thus, obtained samples from patients 6 to 18 months before a diagnosis of colon cancer. These samples have been distributed among 10 institutions for analysis using a variety of proteomic techniques. After the initial analysis, data will be collected and integrated to identify potential biomarkers. Correspondingly, sera from mouse models of cancer at defined stages is also being collected and analyzed, and the combination of human and murine samples increases the probability of identifying useful biomarkers.

The Genetics and Epigenetics of Cancer

Although genetic alterations within the tumor play an important role in tumor biology, genetic variants in the host also contribute
to tumor development, or lack thereof. Peter Kraft (Boston, MA) discussed the advantages and disadvantages of genetic association studies, specifically single nucleotide polymorphisms (SNP). In short, the limitations are (a) rare variants may be undetectable; (b) linkage disequilibrium may lead to false association due to physical proximity; and (c) genetic architecture may be too subtle in that association may be affected by multiple factors, including gene-gene and gene-environment interactions. Despite these limitations, Kraft argued they can be overcome by careful study design and large sample sizes. To acquire these large sample sizes, Kraft et al. are participating in multicenter collaborations including Breast and Prostate Cancer Cohort Consortium and the Cancer Genetic Markers of Susceptibility Study. The clinical impact of studying SNPs was reinforced by Nobuyuki Hamajima (Nagoya, Japan). He found that polymorphisms in the PTPN11, IL-2, and IIL3 genes are predictive of the development of precancerous, gastric atrophy following infection with *Helicobacter pylori*.

Epigenetic changes often occur in cancer resulting in changes in gene expression, and recently, several array-based screens have been developed to examine promoter methylation. Stephen Baylin (Baltimore, MD) introduced the concept of the cancer "hypermethylome," an important epigenetic aspect to the cancer genome. He used microarray analysis comparing histone deacetylase inhibitors (HDACi) and a combination of HDACis and 5-deoxy-azacytidine to identify the population of genes that were aberrantly hypermethylated in cancer cells. He characterized the population of genes in which expression could not be restored by HDACis alone, but 5-deoxy-azacytidine could rescue.

Minoru Toyota (Sapporo, Japan) examined the role hypermethylation of genes involved in *WNT, Ras*, and *p53* signaling in gastrointestinal cancers. In his studies, he identified CHFR (checkpoint for forkhead associated and ring finger) as potential cancer therapy targets. The CHFR promoter is abnormally methylated in a variety of cancers, and re-expression of CHFR reduces NF-κB activity. Collectively, these investigators concluded that re-expression of hypermethylated genes is sufficient to reactivate tumor suppressor pathways and suggested methylation as a potential therapeutic target.

**Oncogenic Pathways**

Advances in technology to identify protein-protein interactions provide an important avenue to unravel interconnected protein networks in cells. Using tagged cDNAs as baits followed by liquid chromatography tandem mass spectrometry analysis in a high-throughput format, Tohru Natsume (Tokyo, Japan) has shown the feasibility of identifying previously unknown proteins in complexes involved in processes such as the cell cycle, calcium signaling, apoptosis, and proteosome assembly.

The use of genetically altered mice has become critical to identifying complex interactions between signaling pathways and its impact on biological processes. Andrea I. McClatchey (Charles-town, MA) used genetically altered mice to discover the unusual role of the neurofibromatosis tumor suppressor NF2-merlin in cytoskeletal structure and its relationship to the epidermal growth factor receptor signaling. Masayuki Yamamoto (Sendai, Japan) discussed the molecular mechanisms of the transcription factor GATA-1 regulation of hematopoietic development. He underscored the importance GATA-1, specifically NH2-terminal deletions of GATA-1, in acute megakaryocytic leukemia. Issay Kitabayashi (Tokyo, Japan) discussed proteins associated with the acute myeloblastic leukemia transcription factor AML1 complex and followed the relationships between the histone acetyltransferase MOZ and the protein kinase HIPK2 using genetically altered mice. Takeshi Imanura (Tokyo, Japan) described the use of bioluminescence to examine the effect of a transforming growth factor-β inhibitor, Ki26894, on tumor metastasis in mouse models. *In vivo*, Ki26894 decreased metastasis and increased cell survival. Collectively, these speakers emphasized the importance of understanding the signaling pathway in a whole organism context to identify the complexities and interrelationships involved in modulating a specific pathway.

**Cell and Molecular Biology of Cancer**

Advances in understanding the basic molecular and cellular processes that are modified in cancer have resulted in significant new therapeutic targets. The response to DNA damage is a critical function in normal cells that is modified by cancer cells. Fumio Hanaoka (Osaka, Japan) discussed translesional synthesis and characterized defects of polymerase eta in xeroderma pigmentosum patients. Geoffrey Wahl (La Jolla, CA) addressed advances in the understanding of *p53* regulation by *Mdm2* and *Mdm4* and presented evidence that these regulators of *p53* have potential as drug targets. He also used mouse models and quantitative approaches to show that *p53* activation likely requires a positive feedback loop in which *Mdm2* degrades *Mdm4*, which seems to be an important *p53* transcriptional antagonist.

The molecular determinants of cancer stem cells are now becoming understood, providing new opportunities for the treatment of cancer. Stephen Baylin presented the idea that cancer stem cell properties may be a result of epigenetic changes that result in a chromatin structure often seen in embryonic stem cells. Jane Visvander (Victoria, Australia) described the identification and isolation of Lin-CD24+/CD29hi mammary stem cells and showed that these cells share the same markers as the aggressive basal subtype of breast cancer. Catriona Jamieson (La Jolla, CA) described the role of JAK2 in hematopoietic stem cell differentiation and explained the potential benefits of JAK2 inhibitors for treatment of polycythemia vera and early prevention of leukemia development. The role of N-cadherin in inducing entrance of quiescent hematopoietic stem cells into the osteoblastic niche was discussed by Tosho Suda (Tokyo, Japan). He also proposed that HIF1α mediates adaptation to hypoxia and allows stem cell to remain in quiescence in their hypoxic niche.

Altered glucose metabolism in cancer cells, known as the “Warburg effect” has recently re-emerged as an important area of research and was extensively discussed. Lewis Cantley (Boston, MA) addressed the role of phosphoinositide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) in cancer cell growth. His conclusion was that mTOR is involved in glucose metabolism, and that altered metabolism occurs before the development of neoplasia. In addition to being activated by PI3K, mTOR is up-regulated by HIF-1. Under hypoxic conditions, mTOR is up-regulated and activated, resulting in a shift to glycolysis.

Hiroyasu Esumi (Kashiwa, Japan) proposed an anti-austerity therapy for targeting cancer cells. Specifically, he suggested targeting the ability of cancer cells to live under hypoxic conditions and nutrient starvation. This is especially interesting for pancreatic cancer, which is currently often untreatable and a highly hypovascular disease. Pancreatic cancer cells are selected based on their ability to grow under hypoxic conditions when nutrient starved.
Removing this ability to thrive under hypoxic conditions leads to cancer cell death. Thus, compounds capable of blocking anaerobic metabolism, such as pyrvinium pamoate, may be therapeutically useful.

It has been known for some time that a host’s immune response, including inflammation, influences tumor biology. Keynote speaker Tadatsugu Taniguchi (Tokyo, Japan) detailed the role of IFN regulatory factors (IRF), specifically IRF5 in tumor development. He found that the tumor-suppressive effects of IRF are mediated through IRF5. Lisa M. Coussens (San Francisco, CA) presented data indicating that carcinoma formation is regulated by humoral immunity. B/T cell–deficient mice exhibit reduced cancer incidence due to failure to activate and/or sustain chronic inflammation that results in deficient angiogenesis and epithelial hyperproliferation. Introduction of educated B cells or serum isolated from cancer-prone transgenic mice into B/T cell–deficient transgenic mice rescued these defects. Furthermore, immunosuppression mediated by rituximab slowed cancer progression in a limited clinical study of colon cancer patients.

**Experimental Modeling of Human Cancer**

As one speaker, Lewis Chodosh (Philadelphia, PA), quoted Dr. George Box, “All models are wrong. Some are useful.” There have been many valuable insights garnered from animal models of cancer, and several speakers described biological insight from advances in animal models of cancer. Dr. Chodosh showed how transgenic mice expressing an inducible oncogene in mammary epithelial cells could be used to study tumor reoccurrence, dormancy, and response to treatment. Upon oncogene expression, tumors form; then upon oncogene repression, tumors regress. Some tumors re-emerge. By comparing genes in recurrent tumors to primary tumors driven by Wnt, it was shown that SNAIL is up-regulated 10-fold in the recurrent tumors. Breast cancer survivors who have increased expression of SNAIL relapse sooner than women who do not, leading to the conclusion that SNAIL represents a potential target in recurrent breast cancers.

Masae Tatematsu (Nagoya, Japan) discussed the importance of finding the appropriate model system for in vivo studies. He recapped why Mongolian gerbils provide a much better model animal than mice for the study of H. pylori–induced gastric cancer.

In addition to animal model systems, the marriage of *in vitro* and *in silico* models presents enormous opportunity for quantitative dissection of variables that are critical for cancer development and progression. Michiyuki Matsuda (Kyoto Japan) illustrated how fluorescence resonance energy transfer (FRET) probes can be used to determine dissociation and association constants of signaling molecules and develop a kinetic simulation of oncogene activation. Using FRET probes for signaling molecules such as Ras, PIP3, Raf, and Akt, the spatial and temporal regulation of key oncogenic pathways was quantitated *in vitro* and compared with *in silico* models to untangle the signaling networks critical for the oncogenic process.

Valerie Weaver (Philadelphia, PA) characterized the effects of tumor matrix on tumor invasiveness using quantitative *in vitro* bioengineering. She reported that increasing matrix stiffness can lead to enhanced invasion. This enhanced invasiveness is due to the activation of both ERK and P3K resulting in altered activity of both Rho and Rac.

Alexander Anderson (Dundee, United Kingdom) has developed a mathematical model that also indicates a relationship between matrix properties and cancer invasion. This mathematical model is designed to predict tumor growth and invasiveness by adding the stromal parameters of host matrix, matrix-degrading proteins, and oxygen supply. Because this model includes discrete or individual tumor cells as well as multiple continuous variables, it is considered a “hybrid discrete-continuum” model. The model is designed to integrate the complex host-tumor interactions of cancer across multiple space and time scales.

**Translational and Clinical Advances**

There have been numerous advances made in translational research in both cancer prevention and treatment. Ray DuBois (Nashville, TN) discussed the mechanism by which cyclooxygenase-2 (COX-2) can down-regulate prostaglandin dehydrogenase, which functions as a tumor suppressor, and expanded on the possibility of developing COX-2–independent ways to block prostaglandin E2 tumorigenic effects because COX-2–specific inhibitors have been associated with increased cardiovascular risks. Anita Sabichi (Houston, TX) described how COX-2 inhibitors may act as an effective cancer prevention therapy. There are ongoing phase II and III clinical trials using COX-2 as a preventative for bladder cancer.

Antiangiogenic therapies have also been discussed for some time, and improvements and alternative approaches were suggested at this conference. Napoleone Ferrara (South San Francisco, CA) recounted the discovery and success of anti-vascular endothelial growth factor (VEGF) monoclonal antibody therapies. Yasufumi Sato (Sendai, Japan) described the antiangiogenic properties of the VEGF-induced vasohibin. They concluded that, combined with other therapy modalities, antiangiogenic therapies show great promise in the clinic.

Advances have been made in immune-based therapies in the treatment of cancer. Hiroshi Shiku (Tsu, Japan) described harnessing the adaptive immune system, through cancer vaccines and T-cell therapy, to help treat cancer. He has developed a cholesteryl group-bearing hydrophobized pullulan (CHP) delivery system that self-assembles with the antigen protein and activates T cells *in vivo*. Phase I clinical trials of two CHP-based vaccines, CHP-HER2 and CHP-NY-ESO-1, have shown that CHP-based vaccines induced T-cell activation against cognate proteins in all patients and a clinical response in some patients. Tomoki Todo (Tokyo, Japan) discussed the idea of using conditionally replicating herpes simplex virus type 1 (HSV-1) vectors to specifically target tumor cells and provided phase I clinical study results demonstrating the feasibility and safety of this approach. He then went on to show that “arming” the HSV-1 vector by inserting cytokines such as interleukin 12 and interleukin 18 resulted in increased immune stimulation and enhanced tumor cell death.

Bruce Littlefield (Andover, MA) described the development of the synthetic halichondrin B analogue E7389, a novel anti-tubulin compound, from identification through development of a synthetic compound. His presentation illustrated the challenges of drug discovery and how medicinal chemistry can be used to generate more effective compounds in quantities sufficient for clinical trials.

Pharmacogenetics, the study of how genomic variability affects drug response, was introduced by Mark J. Ratain (Chicago, IL). He pointed out the importance of understanding host genomic variability to correctly dose patients with certain drugs. For example, SN-38 (the active metabolite of irinotecan, a topoisomerase I inhibitor used to treat colon cancer) is inactivated by *UGT1A1* in the liver. Some people have lower levels of *UGT1A1* in their livers.
due to polymorphisms in the UGT1A1 promoter and, therefore, have decreased elimination of SN-38. Thus, these patients have a higher risk of toxicity, and a lower starting dose of irinotecan is recommended for such patients in the package insert.

Toyomasa Katagiri (Tokyo, Japan) expanded on the concept of individualized therapy by addressing individual responses to methotrexate, vinblastin, doxorubicin, and cisplatin (M-VAC) as a treatment for invasive bladder cancer. M-VAC leads to severe side effects in some patients, with no therapeutic effect. Using microarray analysis, Katagiri and his group were able to develop a method using 14-gene screen for predicting response to M-VAC. Yoshi Miki (Tokyo, Japan) also presented work showing that gene expression profiles of breast cancer cancers may be used to determine which patients are likely to respond to paclitaxel and docetaxel and those patients who would likely have adverse effects. Continued study and application of screening technologies to the clinic will likely someday lead to increased therapeutic response and avoidance of unnecessary treatment and/or adverse side effects.

Conclusions and Recommendations

The unusual breadth of topics in this conference resulted in an extraordinary perspective on the continuum of approaches brought to bear on cancer research. The importance of each of these approaches, and the synergistic value gained by their integration, became abundantly apparent. Advances in screening for alterations in DNA, RNA, and protein have revealed new genes, gene modifications, and gene products associated with cancer, but require rigorous cellular and molecular biology to determine causal relationships and mechanisms of action. The emerging use of quantitative methods to model cancer development and progression provides an opportunity to begin to integrate diverse biological observations into cohesive, testable hypotheses. Sophisticated genetically altered mice and advanced in vivo imaging technologies have greatly expanded our ability to test these hypotheses within the context of the complexities of cancer as it exists in a living host. Translation to the point of clinical trials remains a challenge and often requires public-private partnerships and multifaceted collaborations to make advances that will impact the lives of patients and those at risk for cancer. It became clear that the development of consortia and the integration of multiple disciplines is required to provide the wide range of expertise required to capitalize on the wealth of information generated by basic cancer research for translational purposes. The international approach so evident in this meeting should be expanded to extend into avenues that integrate the technology, biology, and clinical expertise of investigators throughout the world toward the common goal of eradicating cancer.

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