A future of cancer prevention and cures: highlights of the Centennial Meeting of the American Association for Cancer Research

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Received 16 May 2007; accepted 22 May 2007

The Centennial Meeting of the American Association for Cancer Research (AACR) was held from 14–18 April 2007 at the Los Angeles Convention Center. This meeting brought together a diverse group of over 18 000 researchers working in the fields of basic and applied cancer sciences, and explored how cancer research could be used most effectively to prevent and cure cancer at the earliest possible stage. The goal of the AACR Annual Meeting was to stimulate the dialog between basic and clinical researchers so that the translation of new discoveries might be speeded up for the benefit of cancer patients. Advances in the clinical application of genomics, epigenomics and proteomics to diagnose, monitor and prognosticate cancer development led to a dramatic increase in the number of presentations with a translational focus at this year’s meeting. Several remarkable areas were particularly highlighted in this report, including The Cancer Genome Atlas, cancer stem cells, microRNA and siRNA, targeted therapy and individualized treatment. This article tries to bring attention to some hot topics in the program that are both new and noteworthy. For those who did not attend the meeting, this report may serve as a highlight of this important international cancer research meeting.

Key words: American Association for Cancer Research, cancer stem cells, functional proteomics, microRNA, siRNA

introduction

The American Association for Cancer Research (AACR) Annual Meeting is the world’s largest and most comprehensive gathering of professionals in the cancer field, encompassing basic, translational and clinical research. Over 18 000 attendees from all over the world participated in the 2007 Annual Meeting in Los Angeles from 14–18 April 2007; it featured 46 symposia, over 20 forums, 19 new concepts in organ site research sessions, more than 50 meet-the-expert sessions, over 40 minisymposia, around 6000 abstracts presented in 7 poster sessions, and more than 460 exhibitor booths. The year 2007 is particularly important, as it marks 100 years of the AACR’s fight against cancer. The centennial theme ‘a future of cancer prevention and cures’ carried through the meeting. The number and quality of events at the 2007 AACR meeting were exceptional, and this article serves to bring attention to some hot topics in the program that are both new and noteworthy.

the cancer genome atlas

The open plenary talk started by Dr Ronald DePinho, Chairperson of the 2007 Program Committee, portrayed the history of cancer research in the past century, Dr Francis Collins of the National Human Genome Research Institute (NHGRI) continued the open plenary session with reflections on the impact of The Cancer Genome Atlas (TCGA) project. This is a 3-year pilot program being performed collaboratively by the National Cancer Institute (NCI) and the NHGRI. The goal of TCGA is to comprehensively characterize the relevant genomic changes in the three tumors chosen for the pilot program, including glioblastoma multiforme, squamous cell lung cancer and ovarian cancer. Approximately 500 tumors of each type will be studied and these data will be used to identify and sequence specific altered genes and genomic regions. Uncovering the genomic roots of cancer will provide many new insights into subtypes of disease that are currently lumped together, allowing more precise correlations with prognosis and response to therapy [1, 2].

inflammation and cancer

A link between inflammation and cancer has been suspected for quite some time and is strongly supported by epidemiological studies. Preliminary research presented at the AACR meeting suggested that controlling inflammation might be important in preventing and treating cancer. Bardia et al. [3] analyzed the cancer incidence and mortality of 22 507 post-menopausal women using non-steroidal
regions, the regions were found, one of the DNA copy number-independent breast cancer data, 100 DNA copy number-independent expression profile and that of its neighbors [6]. For each gene a transcriptome correlation score between its for each gene a transcriptome correlation score between its

large-scale analysis of such alterations by comparing characterized. Vallot and co-workers performed an original systematic identification of comparative genomic hybridization and genetics.

While genetic long-range alterations can easily be systematically identified by comparative genomic hybridization methods, long-range epigenetic abnormalities remain poorly characterized. Vallot and co-workers performed an original large-scale analysis of such alterations by comparing transcriptome and genomic data for the same tumor set. This approach was experimentally validated on a set of 57 bladder transcriptome and genomic data for the same tumor set. This approach was then applied to a set of 130 invasive ductal breast carcinomas. The study offered a new class of compounds that could function as potent DNA hypomethylating agents in the absence of incorporation into DNA and that could be effectively used in epigenetic cancer therapy [10].

cancer genetics

Searches for the role of new genes and single nucleotide polymorphisms in the human genome are uncovering both old and novel gene targets that play a role in cancers and provide predictive value in treatments. Combinatorics, epistasis, as well as positive and negative selection of alleles in the human genome are all part of the future direction of this research path. The human genome sequence, polymorphisms in the human population and environmental inputs come together in the new applications in molecular epidemiology and genetics.

molecular mechanism of the signaling pathway

 Activation of Wnt signaling occurs in a significant percentage of human malignancies, particularly colorectal cancer. Moore et al. [11] sought to define the molecular mechanism by which oncogene runt-related transcription factor 1-myeloid transforming gene chromosome 8 (RUNX1-MTG8) might stimulate Wnt-regulated transcription, which was mediated by the T-cell family (TCF) of transcription factors. Structure–function studies indicated that the nuclear receptor co-repressor (N-CoR)/silencing mediator for retinoid and thyroid hormone receptor binding domains of RUNX1-MTG8 were required for transcriptional repression of the p14 (alternative reading frame) tumor suppressor promoter and suppression of the endogenous p14 gene. N-CoR associated with TCFs and co-immunoprecipitation assays identified an interaction between N-CoR and TCF4, one of the key effector proteins of the Wnt pathway. Mapping studies identified a 90-amino-acid segment in the C-terminus of TCF4 that was sufficient for N-CoR binding. It was hypothesized that the fusion proteins that occurred in acute myeloid leukemia target endogenous co-repressor complexes to activate gene expression and contributed to the development of leukemia.

Dealmeida et al. [12] generated a soluble Wnt receptor containing the cysteine-rich domain of the frizzled 8 receptor fused to the human Fc domain (F8CRDhFc) that downregulated Wnt signaling in vitro and exhibited favorable pharmacologic properties in vivo. Potent efficacy was demonstrated using the mouse mammary tumor virus-Wnt1 tumor model under dosing conditions that did not produce notable toxicity in regenerating tissue compartments such as skin and intestine. Similar to the PA-1 cells, the teratoma cell lines NCCIT, Tera-2 and NTera-2 had a functional autocrine Wnt pathway. In vitro F8CRDhFc inhibited both basal and wt3a stimulated signaling in these teratoma cells and in vivo, systemic administration of F8CRDhFc significantly retarded the growth of tumor xenografts derived from cell lines PA-1 and NTera-2. The efficacy of a soluble Wnt receptor was reported to be an antitumor agent, and suggested that further development of soluble Wnt antagonists would have utility in treating human cancer.

The phosphatidylinositol 3-kinase (PI3K) pathway is often aberrantly activated in cancers due to the loss of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) tumor
suppressor or activating mutations in the PIK3CA gene that encodes the catalytic subunit of PI3K. Drugs that target PI3K directly or target protein kinases upstream or downstream of PI3K are entering clinical trials for a wide range of cancers. Studies presented at this meeting provided an overview of how the PI3K pathway was regulated and discussed biochemical mechanisms by which perturbation of this pathway led to inappropriate cell survival and uncontrolled cell growth. PI3K and its downstream target Akt mediate one of the most important survival signaling pathways in cancer cells. Therefore, inhibition of Akt activity is expected to induce apoptotic cell death at multiple levels. In addition, downregulation of the Akt signaling pathway may sensitize cancer cells to cytotoxic oncolytics. This makes Akt among the most validated and attractive targets for the discovery of efficacious therapeutics for the treatment of human cancers.

Lu et al. [13] reported that isooquinoline sulfonamide-based Akt kinase inhibitors exerted potent antiproliferative effect on the U87MG human glioblastoma cells and the Jurkat human T-cell leukemia cells. Both cell lines were PTEN-null with constitutively activated Akt. Treatment of these cells with the isooquinoline sulfonamide class of Akt inhibitor resulted in apoptotic cell death. These results supported the notion that synergistic anticancer action could be achieved by combination therapy using Akt inhibitors and conventional cytotoxic cancer therapeutics.

Perifosine is a novel alkylphospholipid that has been shown to have antitumor activity. Using surface plasmon resonance in vitro, Poradosu et al. [14] found that perifosine inhibited binding of the Akt-pleckstrin homology (PH) domain to artificial membranes containing 3% (mole/mole) phosphatidylinositol-3,4-bisphosphate. It was found that perifosine did not inhibit regulated membrane translocation of the general receptor for the phosphoinositide-1 PH domain or constitutive membrane association of the phospholipase C-δ1 PH domain, further supporting binding selectivity. These studies suggested that perifosine might achieve its effects by specifically interfering with phosphoinositide binding by the Akt PH domain.

PTEN is frequently mutated in a variety of human cancers and disruption of PTEN leads to tumorigenesis in multiple tissues in mouse models. Shen et al. [15] reported that nuclear PTEN was associated with a centromere protein, CENP-C, an integral component of the kinetochore that formed a functional centromere. Moreover, PTEN also controlled DNA repair, it acted on chromatin and regulated the transcription of Rad51. Ectopic expression of either PTEN or Rad51 in PTEN-null cells suppressed the incidence of spontaneous double-strand breaks, suggesting that the PTEN-Rad51 signaling cascade constituted a crucial double-strand break repair pathway. The findings established the fundamental role of PTEN in the maintenance of chromosomal stability through multiple mechanisms. It was proposed that PTEN acted as a guardian of chromosomal integrity and genomic stability.

cancer stem cells

Stem cells (SCs) can self-renew and differentiate along multiple lineages to generate different tissues. The long-term potential of SCs makes them beneficial for rejuvenating tissues, but also makes them prone to accumulating mutations over time, a process that can lead to cancer. Normal tissue SCs are of great interest in the cancer field because they possess features required for sustained tumor propagation. There is increasing evidence that cancers develop from a small subset of cells termed cancer SCs. These cells are a rare subpopulation of tumor cells that are capable of differentiating into various types of cells within most tumors. They are responsible for initiating and sustaining tumor growth, and are now widely believed to be distinct from the bulk tumor cells and to be responsible for many cases of drug resistance and cancer recurrence. This meeting had a dramatic increase in cancer SC presentations, and there is a growing awareness that effective cancer treatment will require drugs that kill cancer SCs.

Recent research in a variety of tumor systems has given support to the cancer SC hypothesis. At this meeting, Wicha et al. [16] moderated a session during which researchers discussed new discoveries suggesting that stem cells in leukemia, breast and colon cancer were at the root of many tumors. They developed techniques for the isolation and characterization of SCs from human mammary glands and mammary carcinomas. Mammary stem and progenitor cells could be cultured in vitro as floating spherical colonies which they had termed ‘mammospheres’ that were composed of progenitor cells capable of multilineage differentiation, as well as SCs capable of mammosphere formation. Experiments showed that the PTEN and HER2/neu genes that were associated with aggressive breast cancers had SC properties. Their studies provided a conceptual link between hereditary and sporadic breast cancers by demonstrating that both might be initiated by dysregulation of the normal tightly regulated process of SC self-renewal.

In another experiment to investigate the hematopoietic developmental stage and number of mutations required to give rise to cancer SCs, Jamieson [17] conducted a study on chronic myelogenous leukemia (CML). It was found that CD47, integrin-associated protein, was overexpressed in CML cancer SCs and might render these cells impervious to phagocytosis by macrophages.

discovery and application of biomarkers

In contrast to the conventional supervised analysis approaches, Ellis and co-workers focused on the alternative approach of unsupervised clustering where the expression patterns were examined for the purposes of disease classification. Classification of the test set samples was determined from microarray data using a large 1300 gene set [18], and the minimized ‘intrinsic’ gene sets were used for the quantitative reverse transcriptase polymerase chain reaction assay. It was found that the centroid-based algorithms were robust classifiers for breast cancer subtype assignment across platforms and procurement conditions. Their strategy for primer set validation and classification possessed applications
Kinases and phosphatases are dysregulated in many diseases, including cancer. Their manipulation as therapeutic targets has a major potential for therapeutic intervention. However, many compounds selected by enzyme screens or with a phenotypic assay have unexpected effects in intact cells or animals, some possibly due to off-target or a consequence of robust signaling networks and homeostatic controls. Lu et al. [21] reported that a novel approach linking reverse phase protein microarrays (RPMA) to chemical genomics had major strengths in identification and validation of therapeutic targets. Breast cancer cells were incubated with eight pathway inhibitors, including the Akt kinase inhibitor, proteosome inhibitor, mTOR inhibitor, cdk2 inhibitor, MEK inhibitor, epidermal growth factor receptor (EGFR) inhibitor, BCR-ABL inhibitor and p38MAPK inhibitor. The EGFR inhibitor effectively and specifically abrogated EGF-induced and EGFR-dependent signaling events. In contrast, the cdk2 inhibitor appeared to display broad off-target effects. The experiment not only confirmed and delineated an mTOR–cell surface receptor–Akt feedback loop, but also identified a novel feedback loop centered on Akt. This study provided a novel approach for target discovery, network delineation and strategies to clarify the understanding of drug action effects on signaling networks.

**functional proteomics**

The RPMA system developed at the NCI-Food and Drug Administration (FDA) Clinical Proteomics Program has generated proteomic profiles from clinical biopsy specimens measuring the abundance and activity of key regulators. Mundinger et al. [22] generated a single set of RPMAs with 91 serial patient biopsies from 16 patients with different cancers. Data were interpreted using three published curve-fitting/intensity generation methods: a slope method, D125 and MicroVigene. In receiver–operator characteristic cross-comparison, the slope, D125 and MicroVigene methods displayed area under the curve values of 0.550, 0.825 and 0.600, respectively. These data suggested that the D125 method was the most accurate of the three commonly employed RPMA data analysis methods.

Current analytical and cell biological methods for the analysis of glycoproteins from normal or tumor tissues suffer from a lack of sensitivity and selectivity, and often require the use of harsh conditions that are incompatible with protein analysis. Agnew et al. [23] reported a metabolic labeling approach for the detection of glycoprotein subclasses in tumor tissues using a breast cancer animal model. The two-step labeling technique involved the metabolic incorporation of unnatural azide-modified sugars into protein glycans and subsequent ligation with fluorescent azide-reactive detection probes utilizing the copper (I)-catalyzed cycloaddition reaction between azides and alkynes. This labeling technique was fully compatible with downstream mass spectrometry and enabled the identification of glycoproteins isolated from polyacrylamide gels. This novel ‘click’-based glycoprotein detection strategy provided selectivity, sensitivity and versatility that were unachievable with currently available lectin-based and antibody-based methods.

**cancer vaccine**

Drs Lowy and Schiller [24, 25] reported that on 8 June 2006 the FDA licensed a new vaccine for prevention of cervical cancer and other diseases caused by human papillomavirus types 6, 11, 16 and 18. In their own study, the L1 major capsid protein of the papillomavirus was demonstrated to self-assemble into virus-like particles (VLP) that were capable of inducing high-titer neutralizing antibodies, which suggested that L1 VLPs could be used as both a serological test and a vaccine against human papillomavirus infection. The vaccination with VLPs in animal models was found to provide protection against papillomavirus infection. Subsequent trials demonstrating the safety and efficacy of a multivalent L1 VLP vaccine in humans led to the clinical availability of an FDA-approved vaccine.

**microRNA and siRNA**

MicroRNAs (miRNAs) are evolutionarily conserved, small, single-stranded, non-coding RNA molecules (19–30 nucleotides long) encoded in the genomes of plants and animals that regulate the expression of genes by binding to and modulating the translation of specific mRNAs via RNA interference-like mechanisms. They serve widespread functions as regulatory molecules in post-transcriptional gene silencing and have recently emerged as crucial regulators of gene expression, development, proliferation, differentiation and apoptosis. Vertebrate genomes are predicted to encode as many as 1000 unique miRNAs [26], which are predicted to regulate expression of more than 30% of genes [27]. More than 470 human miRNAs have been publicly identified, and a number of these genes have been implicated as oncogenes and tumor suppressors involved in oncogenesis. Clearly, miRNA expression signatures are invaluable and they hold great promise in human disease characterization, as diagnostic markers for tumor classification and biomarkers, as well as potential prognostic indicators for chemotherapy.

RNA interference (RNAi), the biological mechanism in which double-stranded RNA induces gene silencing by targeting complementary mRNA for degradation, is revolutionizing the way researchers study gene function. Targets generally regarded as undruggable by small-molecule or antibody approaches can be effectively inhibited by small interfering RNAs (siRNAs), the effectors of gene silencing. Maraganoare [28] used cell-based screening assays to identify highly potent and specific siRNAs. The RNAi technology was found to be an ideal tool for validating potential targets for therapeutic intervention in vitro.

Macdiarmid et al. [29] reported a technology that has potentially overcome the in vivo tumor cell-specific delivery and toxicity shortcomings through encapsulation and cancer cell-specific targeting of siRNAs. Mouse xenograft studies showed that intravenous...
administration of $10^9$ bispecific antibody targeted EDVs packaged with siRNAs directed against proteins such as kinesin spindle protein or polo kinase 1 resulted in highly significant antitumor effects. Various doses of monkey EGFR-targeted and doxorubicin-packaged EDVs were tested in two separate rhesus monkey toxicity trials and the results showed no signs of toxicity despite five repeat doses. The versatility, safety and efficacy of the EDV potentially paved the way for tailor-made cancer therapy where targeted EDVs carrying siRNAs and/or drugs could be mixed and matched for individual patient needs.

The recently discovered piwi-interacting RNA (piRNA) was also introduced in the presentations at this meeting. The piRNA is a class of small RNA molecules that is expressed uniquely in mammalian testes and forms RNA–protein complexes with Piwi proteins. These piRNA complexes are linked to transcriptional gene silencing of retrotransposons and other genetic elements in germ line cells, particularly those in spermatogenesis. Purification of these complexes has revealed that the oligonucleotides are approximately 29–30 nucleotides long. They are distinct in size from miRNA and are associated with distinct protein complexes [30–32].

## targeted therapy and individualized treatment

Many oncologists believe that targeted therapies are the chemotherapy of the future. This approach began with the cloning of the EGFR cDNA and HER-2/neu and translated the animal oncogene concept into the first specific human oncogene target-directed cancer therapy Herceptin. Subsequent target-driven drug development efforts that employed various genomic analysis strategies led to the identification and validation of Flk-1/vascular endothelial growth factor receptor type 2 (VEGFR-2) as a critical signaling element in tumor angiogenesis, and the development of Sutent/Sunitinib represents a prototypical example for the adaptation of cancer therapeutics from monospecific to multitracked drugs.

Second-generation irreversible inhibitors are still under study to circumvent the acquisition of drug resistance, commonly associated with a second site mutation in the gatekeeper residue within the adenosine triphosphate pocket of the receptor, which reduces binding to the reversible inhibitors gefitinib and erlotinib. Haber and Settleman [33, 34] found that the mutant receptors transduce increased downstream signals, including both pro- and antiapoptotic signals. It was observed that a subset (5–20%) of gastric cancers with high-level amplification of the growth factor receptor Met also exhibited extreme sensitivity to a single-agent demonstration in patients with chemotherapy-refractory colorectal cancer.

Cetuximab also demonstrated antitumor activity in irinotecan-refractory metastatic colorectal cancer (mCRC) in combination with irinotecan [36]. A randomized phase III eribitux plus irinotecan in colorectal cancer clinical trial was designed to demonstrate the impact of cetuximab on survival in EGFR-expressing mCRC patients ($n = 1298$) who failed prior oxaliplatin-based therapy ± bevacizumab. The combination of cetuximab and irinotecan in second-line mCRC resulted in significantly longer progression-free survival and higher response rate than treatment with irinotecan alone [37].

Lapatinib is a potent, oral, small-molecule dual inhibitor of both EGFR (ErB1) and HER2 (ErB2) tyrosine kinases. The results of pre-clinical and phase I clinical studies led to five phase II/III studies investigating the role of lapatinib in refractory advanced/metastatic HER2-positive breast cancer that progressed following therapy with trastuzumab. Results demonstrated that lapatinib, through its potent, selective and reversible dual mechanism of EGFR/HER2 inhibition, proved to be efficacious in the clinical setting [38].

Approved small-molecule anticancer agents sunitinib and sorafenib provide clinical benefit by inhibiting multiple tyrosine kinase receptors involved in angiogenesis and tumor cell proliferation. Selective inhibition of the VEGFR-2 pathway may offer similar clinical benefit while restricting associated toxicities of pan-specific blockers. This was successfully demonstrated by a phase I study on CT-322 (a selective blocking agent of VEGFR-2) in cancer patients [39].

## challenges and perspectives

High-throughput technologies have revolutionized cancer research, leading the way to the ‘-omics’ era. Genomic and proteomic technologies provide unprecedented resolution in classifying human malignancies in clinically meaningful ways. Empirical associations between fingerprints of gene expression have led to useful biomarkers in patient stratification and prognostication, but recent advances now permit the identification of biochemical pathways and regulatory nodes that can be targets for therapeutics. Cancer can now be investigated with a systems perspective in mind, which includes epigenetics, genomics, transcriptomics and proteomics. This evolution in computational, statistical and analytical approaches for making sense of the amassed information, often in terms of existing data or in concert with multiple levels of data. Integrative analysis of multidimensional and heterogeneous molecular data may enable scientists to pinpoint pathways, networks and predictive markers that distinguish cancer from benign conditions as well as define clinical subtypes of malignant disease [40–42].

The wealth of information about the causes, growth and spread of cancer allows us to make substantial strides toward improved patient care and outcomes. However, cancer still kills about a dozen people worldwide every minute of every day. Fulfilling the promise of personalized molecular medicine...
is a major challenge for the next decade. The AACR meeting described approaches to the comprehensive analysis of DNA, RNA and protein that might allow us to identify patients likely to respond to novel targeted therapeutics with minimal toxicity and greatly improving outcomes. Energies should be focused on making cancer a national and international priority. The AACR Centennial Meeting has been closed with satisfactory accomplishments, but the fight against cancer is still ongoing. Citing the appeal made by Dr DePinho in his open plenary speech to the scientific communities: ‘Let’s make cancer history’.

classification of interest statement
None declared.

references