Oncogenomics 2005 Meeting Report: Dissecting Cancer through Genome Research

Ellen G. Feigal, 1 Nicholas C. Dracopoli, 2 and Jeffrey M. Trent 1

1Translational Genomics Research Institute, Phoenix, Arizona and 2Bristol-Myers Squibb, Pharmaceutical Research Institute, Princeton, New Jersey

Abstract
The Oncogenomics Conference was held on February 2 to 5, 2005 at the Omni San Diego Hotel, San Diego, CA. The meeting chairpersons were Dr. Jeffrey Trent (Translational Genomics Research Institute, Phoenix, AZ) and Dr. Nicholas Dracopoli (Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ). This fourth conference sponsored by the AACR brought together a diverse group of scientists working in the fields of genome research, cancer biology, and epidemiology, and explored how genomic research can be used most effectively to impact the clinical response to cancer. Advances in the clinical application of pharmacogenomics to predict response to oncology therapeutic modalities led to a dramatic increase in the number of presentations and posters with a clinical focus at this year’s meeting. The keynote address was given by Dr. William Evans (St. Jude Children’s Hospital, Memphis, TN) who discussed the pharmacogenomics of acute lymphoblastic leukemia as a cancer paradigm. (Cancer Res 2005; 65(19): 8587-90)

Accelerating Genomics into Clinical Practice

The conference began with an educational session chaired by Dr. Ellen Feigal [Translational Genomics Research Institute (TGen), Phoenix, AZ]. She articulated a vision for 21st century medicine that centered on therapy tailored to the individual's and tumor's genetic and molecular makeup; challenges currently facing us in early detection, diagnosis, drug development, and treatment monitoring; the clinical needs, and the opportunities that scientific advances and technology provide; and concluded with some goals to consider to reach our vision.

Issues and questions posed to the presenters from the four companies included: what are the different scientific, clinical, and regulatory issues and pathways to consider in developing biomarkers that can help in the development of new treatments? How do we identify the individuals more likely to benefit from prevention, screening, and treatment interventions? How can we have an early warning monitoring system to detect recurrence? What are the strengths/limitations in the technology platforms? What is the reproducibility and performance of these tests? How are we validating these technology tools, and what is their applicability to the clinical setting?

Presentations from experts in bringing diagnostics into the marketplace addressed various aspects of these issues. Dr. Rene Bernards (Agenda, Amsterdam, the Netherlands) described the 70-gene DNA microarray profile in breast cancer for prediction of recurrence and overall survival. This test, which requires fresh-frozen specimens, was evaluated retrospectively in test and validation sets, and is being evaluated in the context of a prospective clinical trial. The test is marketed in Europe and is being distributed through a reference laboratory in the U.S. Dr. Steven Shak (Genomic Health, Redwood City, CA) described a 21-gene RT-PCR assay in breast cancer for prediction of recurrence and chemotherapy benefit. This test utilizes paraffin-embedded tissues, and was tested retrospectively in test and validation sets, and is being marketed. Dr. John Sninsky (Celera Diagnostics, Alameda, CA) summarized the challenges, opportunities, next steps, and illustrative examples in moving translational cancer markers from fundamental and applied research to diagnostic assays for clinical practice, and Dr. Nicholas Dracopoli (Bristol-Myers Squibb, Princeton, NJ) provided examples of pharmacogenomic and diagnostic applications in cancer drug development.

The discussion raised more questions that require intensive consideration. These included questions on whether there was overlap in the genes being used by the different breast cancer assays, how these genes were initially identified and selected, and the roles these genes play in the cancer development pathway. In addition, a critical aspect raised was the role of clinical trials in moving these assays to the clinic, and the reproducibility and performance characteristics of these tests which are dependent on the quality of the specimens obtained and how the specimens are handled. The regulatory pathways mandate clinical studies, but not necessarily clinical trials, and the pathway depends on the uses for which the test is being marketed; however, in order for the tests to be widely accepted and adopted into clinical practice, clinicians may want more evidence-based data derived from larger studies on well-annotated tumor specimens or the evidence obtained during the conduct of clinical trials.

Genomics: Technology and Future Directions

This session, chaired by Dr. Elaine Ostrander (National Human Genome Research Institute, Bethesda, MD), focused on technology innovations. Dr. Michael Zody (Broad Institute of MIT and Harvard, Cambridge, MA) discussed the current status of the canine genome sequence, highlighting the fact that a first pass assembly is now complete with >50% of her genome. He concluded with a discussion of how this information can be used to facilitate searches for cancer genes that have proven elusive in humans, particularly those associated with osteosarcoma.
Dr. Gerald Radich (Fred Hutchinson Cancer Research Center, Seattle, WA) demonstrated compelling microarray data that allows clinicians to predict the clinical course of patients with various forms of leukemia following bone marrow transplantation. Chronic myelogenous leukemia, a stem cell disease, is an excellent model for the study of molecular biology because virtually all cases are characterized by the rearrangement of the bcr and abl genes, creating a novel fusion tyrosine kinase. The disease undergoes stereotypical progression from chronic phase through accelerated phase and ends in blast crisis. Dr. Radich demonstrated how PCR can be used to detect bcr-abl with a sensitivity of one chronic myelogenous leukemia cell in a background of a million cells. This has allowed investigators to examine chronic myelogenous leukemia cases that appear to be in remission after therapy, and predict those destined to relapse that still have minimal residual disease. In addition, the quantitation of bcr-abl after therapy has been shown to predict long-term outcome early after therapy. Indeed, quantitative PCR has become the first molecular surrogate of outcome, and is being used in clinical studies as an endpoint, rather than survival. Dr. Radich then showed several microarray experiments aimed at addressing the molecular underpinnings of the disease. Dr. Radich explained how many patients who display an initial response to Gleevec become resistant due to a point mutation in the abl domain that prevents binding to Gleevec. Dr. Radich discussed new methods to perform quantification of genes involved in progression and detection and methods to detect point mutations involving both microfluidics and novel gene expression systems.

Dr. Kelly Frazer (Perlegen Sciences, Mountain View, CA) and her colleagues have been looking at individual differences in DNA variation in the human genome. One recent study involved typing >1.5 million genotypes on a panel of individuals representing African, Asian, and Western European ancestry. Their results indicated that these single nucleotide polymorphisms captured most of the common genetic variation that occurred in these populations as a result of linkage disequilibrium. They observed a strong correlation between extended regions of linkage disequilibrium and functional genomic elements. Finally, they concluded that their data could be used for exploring many questions regarding the causal role of common human DNA variation in complex human traits as well as for investigating genetic variation within and between human populations. In other recently published work, the same group has demonstrated the utility of pooling strategies to identify candidate regions for association with complex traits like HDL levels. In one published study, DNA from individuals with low and high HDL cholesterol levels was pooled separately, and each pool was examined using a high-density oligonucleotide array. A subset of single nucleotide polymorphisms with the largest estimated allele frequency differences between low and high HDL cholesterol groups was chosen for individual genotyping. Four single nucleotide polymorphisms in a single haplotype block within the cholesteryl ester transfer protein gene interval were significantly associated with HDL cholesterol levels. This exciting result demonstrated the utility of both the pooling strategy and the genomic architecture information collected by this group to date in understanding the genetic basis of complex traits.

The session concluded with a talk by Dr. Joseph Nevins (Duke University Medical Center, Durham, NC) who highlighted a strategy to resolve genomic heterogeneity that exists in tumors by using multiple gene expression patterns that are associated with various tumor types and then using statistical tree-based classification systems for providing a framework to depict the many patterns that describe particular tumors. Innovations included the introduction of tree models that explicitly address and incorporate retrospective design and the use of nonparametric Bayesian models. This approach provided a much needed mechanism to combine both genomic and clinical data to develop the most accurate descriptor of a particular tumor type. Dr. Nevins has applied similar strategies to identify gene expression phenotypes of oncogenic signaling pathways and his work has focused on the Ras, Myc, and Rb-E2F pathways. They can now predict pathways of deregulation that coincide with various clinical outcomes for breast, ovarian, and lung cancer. As a result, much like the work of Dr. Radich, they now have the potential to predict response to targeted therapeutics.

### Mathematical Oncology and Pathway Prediction

Dr. Todd Golub (Broad Institute, Cambridge, MA) chaired this session which was focused on mathematical approaches to extracting biological knowledge from the multiplicity of changes observed in complex microarray experiments. The first talk by Dr. Pablo Tamayo (Broad Institute, Cambridge, MA) discussed gene set enrichment strategies to identify patterns in complex biological data. The second talk by Dr. Andrea Califano (Columbia University, New York, NY) described the use of Algorithm for the Reconstruction of Accurate Cellular Networks (ARACNe) to reverse-engineer regulatory pathways using c-MYC as an example to seed one of the more complex networks in eukaryotic cells. The third presentation by Dr. Gustavo Stolovitzky (IBM, Yorktown Heights, NY) discussed a model of p53 response to DNA damage. A mathematical model of the repair processes for double-stranded DNA breaks was developed using the ataxia-telangiectasia (ATM), p53, and Mdm2 genes was developed showing how ionizing radiation induces a phosphorylation cascade within this autoregulatory feedback loop. The final presentation in this session by Dr. Zoltan Olvai (University of Pittsburgh, Pittsburgh, PA) discussed a range of transcriptional regulatory units in Escherichia coli and showed how microarray analyses could be used to deconvolute specific regulatory pathways responding to differential environmental stimuli. In all, each of these presentations gave different approaches to the analysis of complex microarray data, and discussed various analytical methods to identify and analyze the biological basis of features detected within these data sets.

### Molecular Cancer Biology

Dr. Carl Barrett (National Cancer Institute, Bethesda, MD) chaired this session focused on the intersection of genetics and cancer biology, and lessons learned from AIDS. Tumors have been compared with wounds that do not heal, suggesting that these processes may share analogous regulatory mechanisms. To determine the extent to which renal regeneration and carcinogenesis share common mechanisms, Drs. Barrett and Riss undertook an extensive molecular and bioinformatics analysis of gene expression in renal regeneration and repair in a C57BL/6 mouse model and of human renal cell carcinoma. Comparison of the renal regeneration and repair gene expression profile with the profile of renal cell carcinoma reported in the literature reveals two expression signatures: a substantial concordant signature and a distinct discordant signature. While the biological functions of the concordant signature indeed support the view of “cancer as wounds”, the discordant signature points at processes, pathways, and genes that differentiate cancer from wounds. Among these
are the extracellular space, glycolysis, and fatty acid metabolism, mRNA maturation and transcription, DNA repair and/or stress response genes, angiogenesis, morphogenesis and survival signals as well as the insulin-like growth factor-I and the HIF1a pathway. Previous studies compared the gene expression of renal cell carcinoma with the adjacent normal resting tissue, possibly missing the important phenotypic similarities and differences between renal cell carcinoma and renal regeneration and repair.

Bioinformatics comparison of gene expression patterns in renal regeneration and repair and renal cell carcinoma confirms the similarities as well as identified differences between wound healing and cancer. The finding of genes that are regulated in discordant or opposite directions provides new insight into the critical changes that result in malignant growth compared with tissue repair and healing. These results could potentially lead to the development of more effective diagnostic and therapeutic strategies to treat cancer as well as wound healing.

Dr. O’Brien’s presentation summarized the fruits and application of a 20-year-long project to discover AIDS restriction genes, human genes with polymorphic variants that influence the outcome of HIV-1 exposure and/or infection. To date, there are 20 such loci described that involve HIV entry, immune response, or cytokine signaling, slowing or speeding the pace of HIV replication and associated pathogenesis. The lessons learned from these studies involving candidate gene loci are being applied to next-generation gene discovery projects in AIDS, cancer, and other human complex diseases. The ability of HapMap-based association with the discovered AIDS restriction genes was affirmed and new methods that track operative loci exploiting historic linkage disequilibrium in modern ethnic groups was reviewed. In summary, the prospects for gene discovery of many more loci in AIDS and in complex multifactorial cancers are promising.

Clinical Applications of Genomics

These three sessions, chaired by Drs. Laura van’t Veer (Netherlands Cancer Institute, Amsterdam, the Netherlands), Rafael Fonseca (Mayo Clinic, Scottsdale, AZ), and Jeffrey Trent (TGen, Phoenix, AZ) were focused on the pharmacogenomic analyses of existing therapies against a variety of different cancers including breast cancer, leukemia, lymphoma, and myeloma.

Dr. Rafael Fonseca chaired the session regarding the current status of direct application of genomics in clinical medicine focused on the hematological malignancies. These studies provided direct evidence of how genomic tools are employed to dissect and understand diseases whose origins are clearly genetic. The discussion was vivid and particularly relevant since the field of genetics and genomics is best exemplified by the advances attained in the last 40 years in the field of hematological malignancies. Since the advent of karyotype analysis, subsequent development of molecular genetics, development of molecular cytogenetic techniques, and lastly, application and validation of high-throughput genomic tools, the field has made enormous leaps in the application of information derived from such analysis.

The first presentation was made by Dr. D. Ransohoff, from the University of North Carolina (Chapel Hill, NC), who stressed the importance of the critical clinical assessment of purported genetic results as valid in the decision-making process for patients. It is clear that, regardless of the method of detection, the rules of validation and evidence requirements have not changed. In particular, he stressed the importance of the stringent clinical evaluation process of results that can ultimately dictate practice. This is of particular importance with the field of gene expression profiling where independent data sets are needed for ultimate confirmation of results. Dr. J. Pollock from Stanford University (Stanford, CA) discussed the application and integration of gene expression profiling in the field of acute leukemia. Acute leukemia is the prototype disease where genomically derived information has been used for the understanding of disease biology, diagnostic classification, prognostic estimation, clinicopathologic correlation, treatment decisions, and ultimately, drug development. At least two such examples of drug development exist; use of retinoid agents in APL and imatinib for chronic myelogenous leukemia. Dr. M. Shipp, from the Dana-Farber Cancer Institute (Boston, MA), introduced the concept of integrating gene expression profiling in furthering our understanding of biology and clinical implications for lymphomas. Analogous to acute leukemia, the B cell lymphomas are best categorized by the creation of disease compartments defined by baseline genomic aberrations. The integration of gene expression profiling with known biologic pathways and disease classification has allowed for a more rational, and targeted approach, for drug development. Lastly, Dr. R. Fonseca, from the Mayo Clinic (Scottsdale, AZ), discussed the implications of new discoveries in the field of multiple myeloma. In particular, he focused on the advent of a genetics-based classification of myeloma derived from the presence of chromosome translocations that involve the IgH locus and aneuploidy. This has lead to a more in-depth understanding of disease pathogenesis, prognosis allocation, treatment decision (e.g., appropriateness of stem cell transplant for patients with FGFR3 deregulation) and ongoing efforts in drug development (specific translocation of small-molecule inhibitors).

Pharmacogenomics and Drug Discovery

This session was chaired by Dr. Nicholas Dracopoli (Bristol-Myers Squibb, Princeton, NJ), and Dr. Matt Myerson (Dana-Farber Cancer Institute, Boston, MA) led off the session with a discussion of the role of activating mutations in the epidermal growth factor 1 (EGFRI) gene in lung adenocarcinomas. These mutations appear to be highly correlated with response to small-molecule tyrosine kinase inhibitors such as erlotinib and gefitinib. Clinical trials focused on patients with epidermal growth factor–activating mutations are ongoing, although the phase III trial showed no overall benefit for gefitinib. Dr. Edwin Clark (Bristol-Myers Squibb, Princeton, NJ) described the use of transcriptional profiling analysis of both preclinical models (cell lines and xenografts) and pretreatment biopsy samples to identify candidate gene expression markers that predict response to cetuximab. Gene expression profiles derived from preclinical models were described for cetuximab response in colorectal cancer and non–small cell lung cancer. These markers are now being tested prospectively in phase II monotherapy studies in colorectal and non–small cell lung cancer trials, and in combination therapy with carboplatin and taxol in phase III non–small cell lung cancer trials. Dr. Stephen Friend (Merck, West Point, PA) gave a broad overview of integrated methodologies for linking molecular profiling data to clinical outcomes in different tumor types. In addition to transcription profiling, he described how siRNA screens could be integrated with global transcription profiling studies to identify novel markers of drug response and to define subsets of patients with enriched response to novel therapies. In the final presentation of this
session, Dr. Louis Staudt (National Cancer Institute, Bethesda, MD) described transcription profiling experiments that defined three major subclasses of diffuse large B cell lymphoma (DLBCL). Each of these three diffuse large B cell lymphoma subclasses have distinct survival rates following chemotherapy and should be treated as distinct disease entities. In addition to defining markers of differential drug response, these data can also be used to define new drug targets in critical molecular pathways that differentiate between the different diffuse large B cell lymphoma subclasses. Activation of the nuclear factor κB pathway is a critical difference between these subgroups, and suggests that development of selective κB kinase inhibitors will be important for some diffuse large B cell lymphoma subtypes.

Genetic Epidemiology

Dr. Elena Martinez (University of Arizona, Arizona Cancer Center, Tucson, AZ) chaired this session, which was configured to highlight some of the latest issues in this field, including genomewide association studies and haplotype analyses.

Dr. John Carpent (TGen, Phoenix, AZ) presented his work involving cooperative studies of prostate cancer among African-Americans. Of significant importance was his study of prostate cancer in Barbados, where the rate of prostate cancer is the highest in the world. Furthermore, the Barbados population has no indigenous descent, providing a sample with less admixture than that found in African-Americans. Dr. Duncan Thomas (University of Southern California, Los Angeles, CA) provided a comprehensive review of haplotype and pathway analysis as well as analytical issues related to genomewide scans. His key points focused on the identification of causal variants and those related to multiple comparison issues in these analyses. Dr. Thomas also presented his thoughts and some of the ongoing work in pathway-driven research, noting that this area is still in its infancy. Dr. Jianfeng Xu’s (Wake Forest University) presentation focused on the application of novel analytical approaches to the search of prostate cancer genes, through his collaboration in the International Consortium of Prostate Cancer Genetics. Efforts to localize prostate cancer susceptibility alleles by using genetic linkage analysis methods have been hampered by a variety of reasons, including incomplete penetrance and genetic heterogeneity.

The discussion that followed the presentations centered on efforts to establish causality in these studies, which is difficult in epidemiological studies given the inconsistencies in the reported findings. Relevant to this issue is the need for functionality of the variants to be investigated; however, there is no consensus on when these studies should be conducted. Another important topic that was raised has to do with what to do with the information we have or will gain in the future. Speakers fully acknowledged that the precise answer is not known at this time. However, commercial companies are already offering genetic testing to the public without an educational component involved in the process. Therefore, the need for public education related to risk associated with these markers was underscored.

Future of Functional Genomics

Dr. Rene Bernards (Netherlands Cancer Institute, Amsterdam, the Netherlands) provided his perspectives on future directions of identifying novel drug targets using large-scale RNA interference screens in mammalian cells. He noted one of the major remaining deficits in our understanding of the human genome is that information regarding gene function is available for only one quarter of the ~30,000 genes. Many of these hitherto anonymous genes are potential targets for the development of new anticancer drugs. It is therefore important to functionally annotate the tens of thousands of genes for which this information is currently lacking. His laboratory has developed functional genetic approaches to obtain information regarding gene function using high-throughput screens in mammalian cells. They have developed both gain-of-function genetic screens (using retroviral cDNA expression libraries) and loss-of-function genetic screens (using vector-based RNA interference libraries) to carry out large-scale genetic screens in mammalian cells, specifically focused on the central growth-regulatory pathways that are most frequently deregulated in cancer. He presented the results of these large scale loss-of-function genetic screens in mammalian cells, and discussed their development of a very efficient way to identify biologically active shRNA vectors in a large population of vectors, a technology that they named "siRNA bar code screening."

Acknowledgments

Received 7/27/2005; accepted 7/28/2005.

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