Abstract

The physiopathology of cancer cells is the result of very complex signaling networks that represent in many cases distortions of the orderly networks regulating the physiology of normal cells. These networks are the consequence of the expression of, or the lack of expression of, genes, mutated or not, which represent the genomic profile of different types of or of individual cancers. The complex signaling pathways, the cross-talks among them, and the redundancies existing for several of them mediate not only the transmission of signals from the cell environment to the nucleus but also that from the nucleus to the other cellular components whose function is involved in cell proliferation, apoptosis, or differentiation. Modern approaches to cancer therapy and also prevention are aimed at identifying new molecular targets, pivotal to the life of the cancer cell, which would provide for specific sites of intervention. In the face of the enormous complexity of the phenomena on which the life of cancer cells is based, it is both difficult to identify unique specific target for intervention and important to develop analytical tools and approaches capable to identify them for further exploitation. This was the main subject of the Symposium. Consideration was given to: (a) tumor genotypic analysis through expression array evaluation and definition of cancer transcriptomes in studies aimed at identifying determinants of specific characteristics of cancer cells; (b) approaches based on the knowledge gained in this analysis that would lead to the visualization of new targets exploitable for antitumor action; and (c) multifactorial analysis of the complex interactions regulating cancer cells and methods to comprehend the complexity of molecular models and validate their functional relevance.

Tumor Genotype Analysis and Definition of Cancer Transcriptomes

Joe Gray discussed genomic evaluation in breast cancer with emphasis on underlying mechanisms and possible intervention. Using archival samples, differences in genome and gene copies were studied analyzing changes in DNA during tumor progression, specifically at the stage of atypical HP, DCIS, and invasive cancer. Measurements of genomic changes showed that the number of aberrations is relatively small in HP, increased during transition to DCIS, and evolved relatively slowly thereafter. Genome instability assessed as cell-to-cell variation in genome copy number using fluorescence in situ hybridization also showed a significant increase during transition from HP to DCIS, with instability remaining high thereafter. These studies, coupled with analyses of telomerase activity, suggested that breast cancers pass through telomeric crisis during transition from HP to DCIS. This would explain the rapid increase in average genome complexity and genome instability that occurs across this transition. Activation of telomerase in DCIS would stabilize the chromosomes and lead to a slower rate of evolution of the average genotype thereafter. Transition of tumors through telomere crisis would be expected to result in substantial genomic variability between clinically similar tumors because of the somewhat random nature of bridge-breakage-fusion events that occur during telomere crisis. Studies of advanced breast cancers using array CGH indeed showed substantial genomic variation between clinically similar tumors. These are represented by both gene amplification and losses as a function of tumor stage. Some abnormalities do occur sufficiently frequently to be of interest as therapeutic targets. Regions amplified in >20% of advanced breast cancers include those encoding MYC, cyclin D1, ERBB2, ZNF217, and cytochrome P450, subfamily XXIV, whereas regions deleted in >20% of breast cancers include cyclin C, cathepsin B, cathepsin C, forkhead in rhabdomyosarcoma, and mothers against decapentaplegic, drosophila, homologue of 4. The frequencies of abnormalities involving ERBB2, ZNF217, and cyclin C are higher in early stage tumors than in late stage tumors, suggesting that these or nearby genes may be important early in cancer development; the ZNF217 gene contributes to immortalization and may be selected early during telomere crisis. Therapeutic agents targeting prominent genes in the regions of amplification are now being developed with initial focus on receptor tyrosine kinase. Herceptin is now established as an effective therapeutic agent against tumors overexpressing ERBB2. However, the objective response rate of ERBB2-positive tumors to Herceptin is <20%. The possibility is being explored that nontarget genomic abnormalities that occur in tumors may influence response to targeted therapeutics and that this may also allow prediction of response to treatment. Recurrent genomic changes may provide attractive targets for specific anticancer intervention.

Todd Golub outlined whole genome approaches to evaluate gene expression in cancer. He examined whether gene expression profiles could be used to identify transcription factor fusion in AML cells. Using oligonucleotide microarrays, he showed that the induction by IFN of the IFN consensus sequence binding factor is suppressed by telomerase gene; as a result of this inhibition, many of the IFN targets are not affected by the cytokine, e.g., the growth inhibition

phosphatase tensom on chromosome ten; RA, retinoic acid; RAR, retinoic acid receptor; SNP, single nucleotide polymorphism; wt, wild type; SCLC, small cell lung cancer; TMA, tissue microarray; ZNF217, zinc finger protein 217.
response to IFNγ is defective, and there is suggestive evidence that one function of the fusion proteins examined is to facilitate immune escape.

The oligonucleotide microarrays coupled with supervised and unsupervised learning methods were used to obtain the expression profiles of several human malignancies. Acute leukemias (ALL and AML) can be distinguished with high accuracy either through unsupervised clustering approaches or using a number of supervised classification algorithms, including Weighted Voting, k-Nearest Neighbors, and Support Vector Machines. Subtypes of ALL could be delineated, such as those ALLs in infants harboring rearrangements of the **MLL** gene, and distinguished from AML; these leukemias represent a distinct class of ALL that are characterized by homeobox gene A4, A5, A9 overexpression and myeloid characteristics. Similar methods were also applied to B-cell lymphomas, in which the response to chemotherapy for diffuse large B-cell lymphoma was predictable based on gene expression alone. The gene expression profiles of embryonal tumors of the central nervous system were also characterized. Medulloblastoma, rhabdoid tumors, glioblastomas, and normal cerebella were distinguishable based on gene expression signatures. Importantly, a k-nn classifier was capable of accurately predicting survival of medulloblastoma patients based on gene expression profiles of the tumors at diagnosis (P = 0.000057). These studies, taken together, indicate that the classification of human cancers is feasible based on gene expression pattern recognition.

Olli Kallioniemi indicated the advantages of integrating biochip technologies in molecular oncology research. About 30,000 genes are predicted to be present in the human genome. In numerous cytogenetic and molecular cytogenetic studies over the past 10–15 years, many recurrent genetic alterations have been implicated in cancer development and progression. However, most of the genes involved in recurrent chromosomal alterations in solid tumors remain unknown, despite the recent substantial progress in genomic research and availability of high-throughput functional genomic technologies. Integration of the “functional genomic view” of the cancer genome with the traditional “(molecular) cytogenetic view” could lead to the identification of genes playing a critical role in cancer development and progression. In breast cancer, candidate target genes and rearrangements must be prioritized in relation to cancer development and target validation, e.g., 34 DNA amplification regions have been identified by CGH. In the case of one of such amplifications at 17q12, the target gene **HER-2/neu** was already discovered in 1983, but targeted chemotherapy was not clinically available until 1998. Many other proteins encoded by amplified genes have been identified as potentially useful targets but must first be functionally evaluated as potentially useful sites of intervention, as well as explored for their clinical impact. Combination of three different microarray technologies (cDNA, CGH, and TMAs) makes it possible to directly identify candidate genes involved in chromosomal rearrangements in cell line model systems and then rapidly explore the significance of these genes as potential diagnostic and therapeutic targets in human primary tumor progression. TMA is based on constructions of punch biopsies from ~1000 paraffin-embedded tissue biopsies that can be arrayed on a microscopic slide. Microscope slides containing >10,000 mapped cDNA clones provide a template for high-resolution CGH analysis of genetic alterations in cancer. Almost 75% of amplification sites found by this technique had already been highlighted by conventional CGH on chromosomes. One can directly compare gene copy number alterations (CGH on cDNA microarrays) with the analysis of expression levels of the same genes by traditional cDNA microarray analysis across the genome. TMA allows rapid visualization of molecular targets in thousands of tissue specimens at a time, either at the DNA, RNA, or protein level. This technology was validated and found very effective in the case of breast cancer where it was possible to show, e.g., that among 668 cases of primary tumor, the coexistence of **HER-2/neu** and **ribosomal S6 kinase** amplification correlated with the worst survival of the patients. In Switzerland, Guido Sauter’s group examined 4,800 tumors representing 135 different tumor types with an antibody directed toward the **HER-2/neu** oncoprotein and found that this gene product and therapeutic target was expressed in tumors other than breast, such as lung and bladder cancer.

Anne-Lise Borresen-Dale described studies of breast cancer aimed at analyzing tumor genotypes by cDNA microarrays and leading to tumor characterization, prediction of response to treatments, and survival. In a study of 90 breast cancer patients with locally advanced disease on a monodrug therapy (14 mg/m² doxorubicin administered weekly), mutations in the **TP53** gene, in particular, those affecting the L2 or 3 domains of the p53 protein, were significantly associated with short survival and lack of response. Of 68 patients with **TP53** wt, 84% achieved partial responses, whereas of 13 patients with p53 mutated in L2 and 3, only 16% responded. However, 55% of the patients with **TP53** mutations affecting the L2/L3 domains with LOH in addition obtained a partial response or stabilization of disease during chemotherapy, suggesting that other defects may act in concert with loss of p53 function, causing resistance to doxorubicin in breast cancer patients. Patterns of gene expression were evaluated in a set of 85 microarray experiments representing tumor from 78 individuals with cancer, 3 with fibroadenomas, and 4 normal breast tissue using cDNA microarrays containing 8102 genes. Of these, 4000 were named genes, 2500 were homologous, and 1500 were unknown genes. The tumors had been characterized previously for mutations, LOH, and amplifications of a number of different tumor suppressor genes and oncogenes, like **TP53, cERBB2**. Fifty-one of the patient samples were from a cohort of patients with locally advanced disease treated with doxorubicin as a monodrug. Different sets of genes were selected from the total set of expression data. The first set consisted of 1753 genes whose transcripts varied in abundance by ≥4-fold from their median abundance in the sample set. Another set called the “intrinsic gene list” consisted of 476 cDNA clones (427 unique genes). These genes showed significantly greater variation among tumors from different patients than between paired samples from the same tumor. Significant analysis of microarrays was used to search for genes that correlated with overall survival. The gene expression patterns observed in two tumor samples from the same individual, taken 16 weeks apart before and after treatment with doxorubicin, were almost always more similar to each other than either was to any other sample. Five subtypes of tumors (two luminal epithelial-derived estrogen receptor-positive tumor subtypes, a basal epithelial-like group, an **ERBB2+** group, and a normal breast-like group) were identified based on variations in expression using the 476 cDNA clones that reflect the “intrinsic” properties of the tumors. Differences in **TP53** mutation frequency between the subtypes indicated an important role for this gene in certain tumor types. Using “significant analysis of microarray” to identify genes that correlated with patient survival, it was shown that most of these genes defined the basic pattern of expression reflective of basal or luminal breast epithelial cells and also reflected tumor cell proliferation rates. Patients whose tumors expressed high levels of either basal epithelial-associated genes or genes in the **ERBB2** amplicon showed significantly worse outcomes. It was concluded that hierarchical clustering analysis of cDNA microarray expression data using genes selected to reflect biological and/or clinical properties of the tumors provides a new basis for tumor classification.

Michael Stratton discussed approaches to genome-wide searches for mutation in cancer through the development of high throughput mutation detection platforms. Projects are designed to detect homozy-
gous deletions, small intragenic mutations (base substitutions and small insertions and deletions), and chromosomal rearrangements in cancer cells. These are all currently based on the adaptation of conventional mutation detection approaches to very high throughput application. Homozygous deletions have been detected using a PCR-sequence-tagged site approach coupled to nongel-based detection of products using a fluorescence-based assay and were found to exist at a substantial number of loci in the human genome. Identifying which of these deletions are targeting tumor suppressor genes, which are in zones of fragility (and the underlying reasons for the fragility) and which reflect noise or polymorphism, is the next challenge.

Andrew Simpson outlined studies aimed at the definition of the cancer transcriptome using ORESTES. Although a draft sequence of the human genome has been produced, all its constituent genes, the transcripts that they generate, or the timing and localization of their expression are far from being identified. All of this information will eventually be derived from careful and exhaustive transcript sequencing, and the collective information may be rightly termed the transcriptome. Added complexity concerns defining variations in sequence, splicing, and expression level linked to cancer. To date, Simpson et al. have generated >1 million partial transcript sequences from human tumors and corresponding normal tissues. These ORESTES sequences complement sequences generated by the National Cancer Institute’s CGAP project in that the ORESTES sequences are generated from the central portions of transcripts, whereas the CGAP sequences are generated from the extremities of transcripts. In addition, whereas the ORESTES data were derived from tumors prevalent in Brazil, those in the CGAP project are derived principally from the tumors of highest incidence in North America. The ORESTES data were generated in the course of the Ludwig Institute for Cancer Research-Human Cancer Genome Project undertaken entirely in Brazil. Because of the complementary nature of the two cancer genome projects, the data have been combined to form an International Database of Cancer Gene Expression that can be found on the Internet, where the data from ORESTES libraries can be directly accessed. All of the transcript data have now been mapped to the draft genome as a means of accurately clustering the sequences into those likely to be derived from the same genes, thus generating the draft cancer transcriptome. The database provides global information on gene structure, transcript variants, tissue specificity, and levels of expression. The cancer-derived transcripts allow the accelerated definition of the transcribed portions of the human genome in general.

Dr. Thomas Gingeras outlined the present status of studies aimed at mapping of the human RNA transcriptome. Empirically generated transcript maps based on the expression profile mature poly(A)+ cytosolic RNAs from three developmentally diverse cell lines (A375, COLO 205, and CCRF-CEM) were presented. Initial results were discussed in detail for the DeGeorge’s Syndrome region of chromosome 22 (22q11.2). The results of array-based hybridization experiments used to derive the map were compared with the sequence annotations derived from the consensus human genomic sequences. Most strikingly, ~70% of the sequences determined to be transcribed were observed distal (i.e., >300 bp) from the boundaries of the annotated sequences (Sanger, Refseq, dBase). Subcellular fractionation of nuclear and cytoplasmic compartments assisted in detecting low copy number RNA transcripts. Maps have been made of RNA transcripts derived from both nuclear and cytoplasmic RNA populations.

Stephen Friend discussed the potential impact of genomic sensor pads in pattern recognition for the discovery and development of drugs. When one uses specific arrays to elucidate specific areas, one learns only about the questions asked in that area. Mammalian cells are, however, much more complex in their patterns of regulation. Indeed, neither transcript levels nor protein levels directly define the functions of genes or the activities of compounds. By using the entire genome as a sensor pad either at a transcript or protein level, it is possible using pattern matching to interpret unknown compounds and genes in terms of known references, if coherent data sets are used. In addition to sensor microarrays and a coherent database as references, there is the need for a decoder. Single oligonucleotides, 60–70 ms, are used to distinguish closely related genes. Similarity metric is much more important than the choice of clustering algorithms. There is comparability between global and local patterns. These approaches are to be used toward finding specific solutions to actual unmet needs in target identification, lead compound optimization, and safety and efficacy determinations required to shorten the overall drug discovery process. Using these approaches, it is possible to get fingerprints related to new compounds, e.g., predictive matches could be identified in a study of 97 breast cancer patients through profiling of RNA samples without assuming the identity of the most important gene nor the mode of action of the drug.

Eric Schadt outlined ways to enhance candidate gene detection via experimental genome annotation and treating transcript abundances as quantitative traits. In a mouse model of allergic asthma with genetically determined expression of complement factor 5, T-helper cell development, with and without interleukin-12 treatment, was evaluated in relation to airway sensitivity. The up-regulation of gene AK000451 was studied in Utah family 1362, and its pedigree was defined. Using exon and tiling arrays fabricated using inkjet oligonucleotide synthesis, 8183 exons annotated on chromosome 22q were detected under different experimental conditions; mRNAs from human cells were labeled with two-color fluorescence and hybridized to individual chromosome 22 exon arrays. Through a newly developed gene identification algorithm, exons were identified that were correlated across condition pairs; other exons with similar expression patterns extended the initially defined region. The groups of coregulated exons thus identified were called expression-verified genes. Absolute probe intensity provided powerful means to identify expression-verified genes. These methodologies can provide accurate gene numbers and detect mRNA alternative splicing. Tiling arrays are effectively used to refine the gene structure identified by exon arrays. Thus, the use of microarray-based exon and tiling arrays provides for a potentially powerful method to detect candidate genes for a variety of complex human diseases, including cancer, that is not restricted to the consideration of only known genes. When this tiling array approach to experimental genome annotation is focused on regions of linkage for a complex trait, it may not only provide a more direct identification of genes underlying the complex trait but may also uncover regulatory mutations through the observation of alterations in gene activity.

### Visualization of Potential Targets Exploitable for Antitumor Action

Charles Sawyers discussed the therapeutic implications of signal transduction abnormalities in prostate cancer. A set of human prostate cancer xenograft models known as LAPC can be used to study the transition from androgen dependence to androgen independence, as well as the process of metastasis after orthotopic injection. Studies characterizing tumor progression have shown that in prostate cancer, PTEN tumor suppressor gene negatively regulated the phosphatidylinositol 3’-kinase/Akt pathway and that tumors lacking PTEN show...
elevated activation of this pathway, *PTEN* also binds scaffold protein MAGI-2, which enhances its ability to regulate signaling to Akt. *PTEN* is mutated in >50% of prostate cancers. Using the yeast two-hybrid system, a membrane-associated guanylate kinase family protein with multiple PDZ domains was isolated using full-length *PTEN* as bait. MAGI-2 contains eight potential protein-protein interaction domains and is localized to tight junctions in the membrane of epithelial cells. PTEN binds to MAGI-2, and MAGI-2 enhances the ability of PTEN to suppress Akt activation. Recent evidence places the FRAP/mTOR kinase downstream of the phosphatidylinositol 3'-kinase/Akt signaling pathway, which is frequently up-regulated in multiple cancers because of loss of the *PTEN* tumor suppressor gene. PTEN-deficient cancer cells were found to be sensitive to pharmacological inhibition of FRAP/mTOR by the rapamycin derivative CCI-779. Loss of PTEN correlated with an increase in activation of the FRAP/mTOR pathway, as measured by S6 kinase activity and phosphorylation of ribosomal S6 protein and initiation factor 4E binding protein 1. *In vitro* and *in vivo* studies of isogenic *PTEN*+/− and *PTEN*−/− mouse cells, as well as glioblastoma and prostate cancer cells with defined *PTEN* status, showed that the growth of *PTEN*-null cells was preferentially blocked by pharmacological FRAP/mTOR inhibition. In nude mice, the growth of prostate cancer allografts was inhibited by CCI-779 through inhibition of cell proliferation, induction of apoptosis, and reduction of the size of cells. Enhanced tumor growth caused by constitutive activation of Akt in *PTEN*−/− cells was also reversed by CCI-779 treatment. These results provide rationale for testing FRAP/mTOR inhibitors in *PTEN*-null human cancers characterized for Akt function.

At the end of his presentation, Dr. Sawyers briefly outlined the current status of knowledge about the potent activity of STI 571 (GLEEVEC) in patients with CML. The 90–95% response rate in these patients is related to the fact that CML cells (Philadelphia positive) are dependent on the activity of B-cell rearrangement/Abelson TK tyrosine kinase for survival, whereas normal cells are not. The compound inhibits this enzyme through its binding to the ATP-binding domain. The response rate to the drug of patients with CML in blast crisis is much less, and it was found that in these cells, the ATP-binding domain of the target enzyme contains mutations that preclude STI 571 from binding to the site (6 of 9 patients); amplification of the gene coding for the enzyme was also seen (3 of 11 patients).

Pier Paolo Pandolfo discussed the control of cell proliferation, survival, and differentiation in the pathogenesis of APL. This leukemia is invariably associated with reciprocal chromosomal translocations always involving RARα gene on chromosome 17. RARα variably fuses to promyelocytic leukemia, PLZF, nucleophosmin, nuclear mitotic apparatus, and Signal transduction and transcription factor 5B genes. These translocations are balanced and reciprocal, thus leading to the generation of X- RARα and RARα-X fusion genes whose products coexist in the APL blast. RA can overcome the block of maturation at the promyelocytic stage and induce the malignant cells to terminally mature into granulocytes. APL associated with translocation of RARα and the PLZF (RARα/PLZF) genes 11;17) shows no response to treatment with RA. PLZF/RARα reciprocal translocations make cells still sensitive to RA. New therapeutic strategies are required to potentiate the effects of RA and overcome constitutive and/or acquired resistance to RA in APL. Specific or selective inhibitors of histone deacetylase, e.g., suberoylanilide hydroxamic acid, when given in combination with RA for 3 weeks, induce remission of APL through action at the transcriptional level. Likewise, phenylbutyrate has a similar effect in combination with RA. Only 40 genes are up-regulated as a consequence of suberoylanilide hydroxamic acid action; inhibition of histone deacetylase can lead to very specific “transcriptional therapy.”

### Complex Interactions Regulating Cancer Cells and Models to Validate Their Functional Relevance

Fumihiko Matsuda outlined current findings pertinent to the genetic epidemiology of human diseases. Although it is supposed that SNP corresponds to a change with an estimate of two SNPs in the coding region of each gene, the actual number of SNPs is much larger in many genes. As an example, he showed the results with *HHIIR23A*, a DNA repair gene, which carries 12 SNPs in exonic part and shows specific differences in their position and frequency between Africans, Japanese, and Europeans. In a cooperative study with the University of Tokyo, 150,000 human DNA fragments, roughly corresponding to 15,000 genes, are under investigation for SNP discovery using DNA sequencing technology. Genotyping of SNP is done by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry mass spectrometry. Studies of the heavy chain of human immunoglobulin, coded in chromosome 14q32.33, were illustrated as an example. The SNP analysis of hypervariable (VH) segments revealed high levels of polymorphism with clear differences among ethnic groups. Association studies of VH haplotypes and autoimmune disorders and infections are ongoing.

Anton Berns discussed the use of new conditional mouse models for the study of sporadic cancer. Specific tumors are induced, and the model systems are interrogated for genetic lesions, phenotype to genotype relationships, oncogenic pathways, modifier screens, and intervention. Cre/Lox-mediated switching of tumor suppressor genes and oncogenes are used to develop new mouse models for a variety of tumors. Both transgenesis and somatic gene transfer are used to express (inducible) Cre recombinase in a controlled fashion. This permits the induction of highly specific tumors within a narrow time window and to correlate specific genetic lesions with phenotypic characteristics. Sensitive *in vivo* imaging techniques are also used to follow tumor growth and metastatic spread in real time in animals. Initially studied are mammary, lung, and skin tumorigenesis using knockout alleles and conditional oncogenes and tumor suppressor genes.

Three recent models were discussed in some detail:

1. **The role of the loss of p16 function on tumorigenesis in mice.** The *Ink4a* locus harbors two tumor suppressor genes, *p16* and *p19Arf*, each of which has been shown to act as a potent tumor suppressor under specific conditions. However, the effects of *p16* loss in an experimental mouse model have not been described. The oncogenicity conferred by introducing a point mutation into the *p16* reading frame as also found in human tumors, resulting into a functionally highly compromised protein with low stability, was assessed. Although the mutation has little effect on the growth of mouse embryo fibroblasts *in vitro*, it conferred a predisposition to cancer, when combined with hemizygosity of 19Arf. Malignant, metastatic melanomas were found with high incidence when the skin of these mice was treated once with dimethylbenzanthracene. This is reminiscent of the tumor predisposition observed in man with inherited inactivating mutations in *p16*.

2. **Models for non-SCLC, SCLC, and mesothelioma were developed through Adenovirus-Cre switching of conditional oncogenes and tumor suppressor genes.** In this way, papillary tumors were induced in a conditional mutant of Kirsten ras, whereas SCLC lesions were found in Adeno-Cre-treated *P53-*/- and *HHR23A* knockin mice. In addition, these later lesions gave rise to metastasis after 6–9 months. The tumor phenotype was dependent on the conditional lesions present, illustrating the cell type specificity of these oncogenic lesions.

3. **Mammary tumorigenesis was achieved by the conditional inac-
tivation of Brca2 and p53 tumor suppressor genes. Using a K14-Cre transgenic line to switch the conditional alleles in epithelial cells, it was shown that Brca2 deletion by itself is insufficient to cause a high incidence of epithelial tumors. However, in combination with a p53 conditional allele, Brca2 loss mediated accelerated tumor formation. In female mice, mammary tumors were the predominant cancer, whereas in males, a preponderance of skin tumors was observed. In compound mutants, carrying one wt and floxed allele, LOH is invariably seen when a p53flox/wt is present, whereas this is occasionally seen with Brca2flox/wt allele, indicating that p53 loss is a more demanding requirement for tumor formation then loss of Brca2 function.

A luciferase-based in vivo imaging methodology was developed using conditional reporter for luciferase with pituitary tumors as few as 1000 cells could be visualized. After reproducible tumor initiation, exponential increases of tumor mass and Doxorubicin-induced delays in tumor progression could be measured.

Lucio Luzzatto discussed PNH, a clonal disorder which provides a model for selection of mutant somatic cells. PNH is an acquired clonal disorder of the HSC, in which somatic mutations in the X-linked PIG-A gene results in the deficiency of GPI-anchored proteins from the surface of blood cells. Although in rare cases, PNH evolves to AML, in the large majority of cases, PNH persists for years or decades as a chronic disorder, in which PNH hematopoiesis coexists with non-PNH hematopoiesis. Clinical and experimental evidence suggests that the expansion of the PNH clone that leads to the clinical picture of PNH results not from an intrinsic growth advantage of the mutated HSC(s) but rather from a selective process that targets and depletes hematopoietic cells with a glycolipid structure anchor on their surface while sparing GPI(−) HSCs. The close association of PNH with Idiopathic Aplastic Anemia, a T cell-mediated autoimmune disease, and the recent finding of an increased frequency of expanded T-cell clones in patients with PNH suggest that this process is driven by autoreactive T cells specific for GPI(+) HSCs.

A round table discussion led by David Livingston concluded the Symposium. The main topic discussed focused on the prediction that the future of cancer therapeutics is likely to be dependent on the development of new molecules affecting specific new targets, genetically and biochemically determined, which had been validated and require clinical assessment both in deciding whether a patient should or should not be treated with a particular agent (the choice will depend on the presence or absence of the relevant target) and in following the response to the drug. When methodologies are developed for the detection of very few tumor cells, how would one go about identifying and then validating molecular targets in a given tumor? How would one identify the drug or mixture of drugs that would be most appropriate for the tumor of an individual cancer patient? How would one carry out specific risk estimates on which to base rational cancer prevention for a given healthy individual? Given the complexity of the parameters to be evaluated and of the methodologies that will likely be needed to do such evaluations, teams of expert clinical investigators representing the necessary collections of technological skills will be needed to perform the relevant applications research in patients. The participation of teams in which multiple people deserve equivalent credit for success is not readily recognized by the current academic system, which traditionally emphasizes individual scientist recognition. Therefore, it would seem necessary to modify substantially the academic credit system. This may require fundamental changes all of the way back to the level of professional education and will represent a formidable task.

In addition to the oral presentations, the Symposium included 13 poster communications, which are summarized on the Internet.2


Appendix. The program committee consisted of the cochairs, David Livingston (Dana-Farber Cancer Center, Boston, MA), Giorgio Parisi (La Sapienza University, Rome, Italy), and Lee Hartwell (Fred Hutchinson Cancer Center, Seattle, WA). In addition to the program committee members, invited participants included: Anton Berns (The Netherlands Cancer Institute, Amsterdam, the Netherlands), Anne-Lise Borresen-Dale (The Norwegian Radium Hospital, Oslo, Norway), Carlo Croce (Thomas Jefferson Medical College, Philadelphia, PA), Thomas Gingeras (Affymetrix, Inc., Santa Clara, CA), Todd Golub (Harvard Medical School, Boston, MA), Joe Gray (University of California, San Francisco, CA), Olli Kallioniemi (NIH, Bethesda, MD), Lucio Luzzatto (Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy), Fumihiko Matsuda (Centre National de Genotypage, Paris, France), Pier Paolo Pandolfi (Memorial Sloan Kettering Cancer Center, New York, NY), Marco Pierotti (Istituto Nazionale Tumori, Milano, Italy), Charles Sawyers (University of California, Los Angeles, CA), Andrew Simpson (Ludwig Institute, Sao Paulo, Brazil), Eric Schadt (Rosetta Inpharmatics, Kirkland, WA), Michael Stratton (Institute of Cancer Research, London, United Kingdom), Thomas Tursz (Institute Gustave-Roussy, Villejuif, France), and John Weinstein (National Cancer Institute, Bethesda, MD).

The posters were presented by Henrie Bruggenwirth (Erasmus University, Rotterdam, the Netherlands), Mario Falchetti (University G. D’Annunzio, Chieti, Italy), Giovanna Chiorino (Institute Mario Negri, Milan, Italy), Laura Ottini (University La Sapienza, Rome, Italy), Massimo Libra (Centro Riferimento Oncologico, Aviano, Italy), E. Alessi (STMicroelectronics, Catania, Italy), Giuseppe Carruba (University of Palermo, Palermo, Italy), Paola Zacchi (National Laboratory CIB Area Science Park, Trieste, Italy), Elisenda Vendrell (Institut de Recerca Oncologica, Barcelona, Spain), Maria Ribas (Institut de Recerca Oncologica), Alberta Bergamo (Fondazione Calle riero, Trieste, Italy), Minna Allinen (University of Oliili, Olliili, Finland), and Enzo Medico (University of Torino, Torino, Italy).

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Thirteenth Annual Pezcoller Symposium: Focusing Analytical Tools on Complexity in Cancer

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