SP 121

Requirements for prospective use of omics-based tests in NCI-sponsored trials

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High-throughput 'omics technologies offer exciting opportunities for new biological insights into cancer with potential for translation into clinical tests useful for prediction of patient outcomes and optimization of therapy selection. Many molecular signatures based on data generated from high-throughput 'omics technologies have been published, but relatively few of these 'omics-based signatures have been successfully translated into clinically useful tests. Adoption of more rigorous development and validation approaches should help to reduce false leads and improve the efficiency with which clinically useful signatures are identified. This discussion will highlight requirements that should be met by omics predictors before they are used in a clinical trial in which they might influence patient care. These requirements include clear description of the intended clinical use, confirmation of the strength and reliability of the preliminary validation results, documentation of clinical feasibility and safety, specification of an appropriate clinical trial design, and adherence to applicable regulatory requirements. As omics-based tests play an increasingly important role in therapeutic decision making for cancer patients, it is important that the methods used to develop and validate these tests be equally rigorous as the process used to develop therapeutics.

SP 126

FLT3 is a stratification factor for targeted therapy treatments in adult and pediatric AML phase III trials

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FLT3 is a class III receptor tyrosine kinase that regulates stem cell differentiation and proliferation. Receptor activation is mediated by ligand mediated conformational alterations leading to receptor dimerization and kinase activation. FLT3 is variably expressed in leukemias and mutations of the FLT3 gene, either by internal tandem duplication of the juxtamembrane dimerization domain (FLT3/ITD) or missense mutation of the kinase activation loop domain (FLT3 activation loop mutation; FLT3/ALM) lead to cytokine independent receptor activation. Although both FLT3/ITD and FLT3/ALM lead to receptor activation, they are biologically and clinically distinct as those with FLT3/ITD have an adverse clinical outcome, whereas outcome in those with FLT3/ALM is similar to those without FLT3 mutations. Prevalence of FLT3/ITD varies by age, where it is rare in young children (<2 years) with increase in prevalence of 25% in those 15−55 years and >35% in older AML patients. FLT3/ITD has been established as a predictor of relapse and poor outcome in AML. Several studies have demonstrated that although presence of FLT3/ITD correlates with poor outcome in chemotherapy recipients, its adverse prognostic significance is mitigated by stem cell transplantation, thus substantiating the role of stem cell transplantation in improving the outcome of this cohort of high risk patients. In addition to its role as a prognostic marker, FLT3/ITD has provided a viable target for directed therapy with small molecule inhibitors. Initial trials utilizing FLT3 inhibitors led to objective but transient clinical response, leading the way to their combination with cytotoxic regimens. Although such trials have demonstrated variable efficacy in treating FLT3/ITD AML, second and third generation FLT3 inhibitors in combination with contemporary chemotherapy have led to substantial improvements in remission induction and provided optimism in improving the clinical outcome in FLT3/ITD-positive patients. Pediatric and adult phase III trials that are either underway or under development incorporate FLT3 inhibitors as well as stem cell transplantation in managing patients with FLT3/ITD. Long term follow up of these patients will determine whether such combination therapies will lead to improved long term survival in AML patients with FLT3/ITD.

SP 135

Biomarkers for targeted therapy selection in non-small cell lung cancer (NSCLC)

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Although notable progress has been made in the treatment of non-small-cell lung cancer (NSCLC) in recent years, this disease is still associated with a poor prognosis for most patients. Modern techniques have facilitated the identification of specific genetic factors that may play a role in disease progression and patient response to therapy, prompting research efforts to identify the clinical predictors of outcome for NSCLC. Recent evidence suggests that the application of a pharmacogenomic approach has the potential to greatly improve survival in certain subpopulations of patients with NSCLC, which could profoundly influence the decision-making process used in evolving treatment strategies for this malignancy. Genomic signatures may improve the currently used prognostic classification based on clinical characteristics. Impressive responses are observed in patients with epidermal growth factor receptor (EGFR) tyrosine kinase mutations following treatment with gefitinib and erlotinib. Indeed, these EGFR TKIs represent now the standard of care for advanced NSCLC with activating mutations. Traslocations in the ALK gene have been recently reported on a subset of lung adenocarcinoma. This genetic alteration has proven predictivity for ALK inhibitors, such as crizotinib, in preclinical models and clinical trials. Other molecular abnormalities in lung cancer that may be exploited for individualized targeted treatment include b-Raf mutations, Her2 mutation or amplification, PI3K mutations, Met over-expression and others. Expression of markers of DNA repair, ERCC1, RRM1 and BRCA1 may are also determinants of response to standard chemotherapy regimens (e.g. cisplatin/gemcitabine), with low levels of mRNA predicting improved survival. The future challenge of chemotherapy of NSCLC relies on the identification and validation of molecular markers that are predictive of drug sensitivity and are helpful in the selection of therapeutic agents best suited to the individual patient. Other relevant issues will be the identification of the optimal drug sequence in combination regimens and the pharmacogenetics of clinically important toxicities. In addition, due to the developments of novel technologies to discover genetic alterations involved in tumor progression, new therapeutic strategies are awaited.

SP 130

Driving discovery through data integration and analysis

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Two trends are driving innovation and discovery in biological sciences: technologies that allow holistic surveys of genes, proteins, and metabolites and the growing realization that analysis and interpretation of the resulting requires an understanding of the complex phenotypic and environmental data regarding the samples from which they were derived. Further, the growing body of biological and biomedical information in the public domain provides outstanding opportunities for leveraging what we already "know" in a systematic way to understand the problems we are studying. Here, I will provide an overview of some of the methods we are using to investigate the complexities of human cancers and to explore how we can use biological data to begin to uncover the cellular networks and pathways that underlie human disease, building predictive models of those networks that may help to direct therapies.

SP 129

International Cancer Genome Consortium: a promising story in pancreatic cancer

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The genetic anomalies occurring in pancreatic cancer, discovered using a candidate gene approach, include common alterations in four genes, KRAS2, CDKN2A, TP53 and SMAD4, and a variety of inactivated genes at a frequency <5% of cases including TGFBR1, TGFBR2 and others. High throughput sequencing methods have paved the way for identification of most coding genetic alterations in pancreatic cancer. The International Cancer Genome Consortium (http://www.icgc.org/) coordinates a large number of research projects with the primary goal of generating comprehensive catalogues of genomic abnormalities in 500 individual tumours from different cancer types of clinical and societal importance. This permits the several types of distinct somatic mutations (insertions, deletions, translocations, gain/amplifications) that occur in the DNA sequence of the cancer genome cell to be identified. The Italian ICGC project focuses on rare pancreatic tumor types and contributes to the Australian pancreatic adenocarcinoma genome initiative. Published data on large-scale genome analysis on limited set of cases showed that pancreatic cancer evolves by accumulating driver mutations in as many as 20–100 cancer genes, and suggest that distinct molecular phenotypes are numerous and in many cases each phenotype accounts for 10% or less. Indeed, a recent reappraisal of pooled expression profiling data showed the existence of at least two distinct molecular subtypes of pancreatic cancer: classical amd quasimesenchymal. This implies that markers useful in subgroups of patients with a specific molecular cancer subtype may not show efficacy in larger disparate molecular phenotype groups. However, specific genomic alterations from sequencing of a great number of cases may permit molecular subclassification and paves the way to personalized therapy and follow-up as well as to the discovery of a classifiers permitting the development of early diagnostic markers, given their presence at the PANIN stage.