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From Genetic Testing to Genome Testing: Technologies and Approaches in Cancer Profiling

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Cancers are common diseases which are among the leading causes of death worldwide, and their incidence is increasing as the population ages. Individual cancers harbor a set of genetic aberrations that can be informative for identifying rational therapies. However, cancer genetic assessment to guide use of therapies has been limited to single biomarkers. Improvements in sequencing technologies and implementation of genome analysis tools have enabled clinicians to identify functional and/or disease-associated genomic variants. Although we have come close to getting an entire genome sequenced for $1000, cancer genome sequencing involves significant challenges including the quality and quantity of samples available, the data analysis and interpretation. There are ways to overcome most of these challenges and get meaningful data. For instance, increasing sequence depth can counter low sample purity and increased ploidy. Sequencing the ends of DNA library molecules can identify discordant pairs representing deletions, amplifications, inversions or translocations; therefore, paired-end reads have become a valuable strategy for cancer genomics. Furthermore, since most genetic abnormalities in cancer are somatic and not germ line, a comparison of a patient's matched "normal" genome is crucial to interpret the alterations identified through deep sequencing. Last but not least, combination of cloud-based and manufacturer installable analytic pipelines together with inclusion of RNA and protein information in conjunction with sequencing data are becoming critical in deciphering the molecular basis of disease providing rationale for targeted, personalized drug treatment. The objective of this talk is to review existing technologies including reversible terminator SBS, semiconductor-based SBS, single molecule RT sequencing, single-strand DNA/RNA nanopore-based sequencing as well as to note emerging technologies. Examples of whole transcriptome analysis including non-coding RNA and whole genome amplification from isolated circulating tumor cells (CTC) in metastatic breast cancer (MBC) patients will illustrate applications of these technologies to deciphering the molecular basis of disease providing rationale for targeted, personalized drug treatment.

Determination of Rare Genomic Variants Leading to Hematological Malignancies Using Next-Generation Sequencing

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Rare hematological malignancies are a heterogeneous group of the disease. Malignant transformation of a hematopoietic stem cell is a result of gradual accumulation of mutations in a number of genes involved in basic cellular processes. One of the main goals in the study of hematological malignancies is the definition of genomic markers crucial for the development of the disease, as well as for recognition of multiple entities characterized by distinct prognosis and outcome of the disease. Application of new high-throughput technologies has enabled better insight into genomic landscape of hematological malignancies. The most important achievement of genome-based medicine is more precise classification of patients with hematological malignancies, based on newly discovered molecular markers, and molecular–targeted therapy, tailored to genomic profile of a disease.

In our studies we applied amplicon based next generation sequencing (NGS) approach, using TruSeq Amplicon Cancer Panel (Illumina, Inc) for analysis of 48 cancer-related genes in primary diffuse large B-cell lymphoma of central nervous system (DLBCL CNS), acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).

Our findings strongly suggested that the *TP53* and *ATM* genes were involved in the molecular pathophysiology of primary DLBCL CNS. Mutations in the *PTEN* and *SMO* genes affect survival of the patients. Additionally, we found that AML and ALL contain small number of genetic alterations, contrary to lymphomas.

While protein-changing variants were found in tyrosine kinase genes, genes encoding tyrosine kinase associated proteins (JAK3, ABL1, GNAQ, and EGFR) and in the methylation and histone modifying genes (*IDH1*, *IDH2*, and *SMARCB1*) in patients with AML, the mutations detected in ALL patients are related to key signaling pathways, primarily on Ras/RTK cascade.

Application of next-generation sequencing technology resulted in the information about genetic profile of each patient. Individual genetic profiling leads to highly specific personalized therapy of hematological malignancies.

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