Acute myeloid leukemia

- Tissues were microdissected, solubilized, and enzymatically digested
- PARADIGM used to reveal shared pathways among patients
- Associations between gene mutations and expression were determined:
  - RNAseq data confirmed the presence of gene mutations
  - DNA sequencing data were processed using Contraster2
  - Transporter software platform encrypted and securely transferred unassembled data from sequencer to
- A sequencing data set of patient-matched tumor-normal samples was analyzed from The Cancer

**Abstract #11093**

- Genomics, Transcriptomics, and Proteomics in the Clinical Setting: Integrating Whole Genome and RNA Sequencing
- With Quantitative Proteomics to Better Inform Clinical Treatment Selection

**Background**

- Next-generation sequencing (NGS) and quantitative proteomics enable the timely identification of a cancer patient’s unique molecular signature, independent of an anatomical tumor type, allowing the identification of clinically relevant targets for informed treatment selection
- Gene panels comprised of 1,000 genes are most often used to guide treatment selection; however, panels do not provide insights into altered protein expression
- To predict the downstream effects of gene alterations, orthogonal technologies such as RNAseq and proteomics are needed
- RNAseq confirms the expression of mutated genes and enables the quantitation of gene expression and what is integrated with RNAseq data using pathway-based modeling algorithms such as PARADIGM can be used to infer protein expression within autophagic-stressed pathways
- Higher spectrometry-based proteomics allows the quantitative measurement of expressed proteins that influence disease progression and sensitivity to therapeutics

**Methods**

- We have developed a platform that integrates whole-exome-wide genome sequencing data of patient-matched tumor-normal samples with RNAseq, quantitative proteomics, and pathway analysis to identify clinically relevant targets

**Panomic Approach to Precision Cancer Medicine**

- DNA Sequencing, RNAseq, Pathway Analysis

**Study Population and Data Set**

- A sequencing data set of patient-matched tumor-normal samples was analyzed from The Cancer Genome Atlas (TCGA) CIG Fat database (https://tcga-data.nci.nih.gov)
- Whole-exome sequencing data/RNAseq data were available for 3,793 patients

**Data Analysis**

- Transporter software platform encrypted and securely transferred unassembled data from sequencer to
- DNA-seq data were processed using Con2rater
- Sample panel activity is defined by 328 genes
- RNAseq data confirmed the presence of gene mutations
- Mutant classified as high-expressed (≥0.3 aikle/hour) and low-expressed (≤0.3 aikle/hour)
- RNAseq expression value calculated using a normal distribution across adjacent normal samples in TCGA;
- "High" expression was 2.0 exome x 3
- Associations between gene mutations and expression were determined:
  - Highly expressed gene mutations (whole exome versus gene panel)
  - Low/medium expression of gene mutations (gene panel)
  - Highly expressed non-mutated genes (gene panel)

**Protocins**

- A number of drugs targeting tumor mutations are approved in cancer indications

**Classification of Tumors Based on Shared Pathways**

- Mutated Targetable/Actionable Genes Across Cancer Types

**Highly Expressed Mutant Alleles: Whole Exome vs Panel**

- Proteomics
- Low/No Expression of Mutant Alleles: Panel

**Panomics Case Study: End-Stage Cervical Cancer**

- Predictive Value of Proteomics: HER2 as an Example

**Panomics**

- HER2 gene amplified 8-fold due to insertion of HPV DNA into patient's genome at chromosome 17
- Patient treated with anti-HER2 therapy, disease stabilization for 1.5 years

**Conclusions**

- Mutations in genes targeted by drugs approved based on anatomy are prevalent in other cancers independent of tissue type
- Expression matters
- Quantitative measurement of HER2 >2200 amol/μg is predictive of longer survival
- PARADIGM platform integrating genomic sequencing with quantitative protein expression analysis informed effective treatment for patient with end-stage cervical cancer with a drug not approved in that tissue type
- Precision cancer medicine will require recategorization of cancers based on their molecular profile and not on tissue type

**References**

- Sedgewick AJ, Benz SC, Rabizadeh S, Soon-Shiong P, Vaske CJ. In collaboration with Vall d’Hebron University Hospital.3
- *Hazard ratio for OS cannot be determined because all patients with >2200 amol/μg HER2 are alive after 6 years of anti-HER2 therapy. NA = not available.
- **References**
  1. Sedgewick AJ, Benz SC, Rabizadeh S, Soon-Shiong P, Vaske CJ. In collaboration with Vall d’Hebron University Hospital.3
  2. *Hazard ratio for OS cannot be determined because all patients with >2200 amol/μg HER2 are alive after 6 years of anti-HER2 therapy. NA = not available.
  3. **References**

**Acknowledgment**

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