Translational Genomics Research Institute
Individualized treatment based on whole-genome sequence

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David W. Craig, Ph.D.  John D. Carpten
Overview

- Clinical Genomics Center
- Leadership
  - Jeffrey M. Trent, Ph.D (TGen). Dan Von Hoff, M.D (Physician)
  - David W. Craig, Ph.D. (Informatics)   John D. Carpten, Ph.D. (Cancer Biology)
- Core premise - Onocology
  - Is molecular profiling using new technologies a rationale approach to increase the “options” available to oncologists for treating cancer patients, namely those who fail standard of care or those patients with otherwise chemo-resistant metastatic cancer?
- Approach
  - Integrative Analysis of whole transcriptome and genome sequencing for treatment when no other clear options are available in the context of clinical protocols
- Ongoing Studies
  - Approximately 50 patients treatments – WGS 2011
  - Triple Negative Breast Cancer (Life Foundation)
  - Rare Cancer Treatment Study (NFCR)
  - Neuroblastoma (Dell)
  - Genetics of unknown etiology
  - Several forthcoming
Protocols/Trials in WGS for Oncology
Providing Support For Clinical Partners through Integrated Analysis of Whole Genome Sequencing

1. Criteria
2. Surgery
3. Clinical Pathology
4. Sequencing
5. Integrative Analysis
6. Tumor Board
7. CLIA Validation
8. Treatment Decision
9. Outcome

Support Layer 1: CLIA
Support Layer 2: Sequencing
Support Layer 3: Informatics

Historical Databases
Goal: Each cancer genome is unique, identify events with clinical utility
Examples
Example 1: Rare Tumor – Metastatic Uterine Transitional Cell Carcinoma

- **NFCR**: Involved Glen Weiss, Winnie Liang, Tyler Izatt, Shripad Sinari, Alexis Christoforides, Ahmet Kurdoglu, Angela Baker, John Carpten, Dan Von Hoff, TGen/SHC (National Foundation for Cancer Research)

- Transitional cell carcinoma of the uterus is highly curable if detected early

- NFCR patient 01-08 diagnosed with Metastatic Uterine TCC

- Sequencing Design and Statistics:
  - Illumina HiSeq2000, Paired-End
  - Tumor: 46X uniquely mappable
  - Normal: 55X uniquely mappable
  - RNA-seq for tumor and normal uterus (~100 million reads)
Rare Tumor – Metastatic Uterine Transitional Cell Carcinoma

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Rare Tumor – Metastatic Uterine Transitional Cell Carcinoma

Charts of Each Chromosome Where DNA Has Been Changed

- CDKN2
- LRP1B
- FHIT
- EGFR
- MYC
- IRS2
- PIK3C3
- TP53
- PRKCA
- UTX

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Rare Tumor – Metastatic Uterine Transitional Cell Carcinoma

Concomitant TP53 W146X, but no KRAS

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- Performed a clinicopathologic, immunohistochemical, and molecular genetic analysis of 19 transitional cell tumors including 13 tumors (5 benign, 7 borderline, and 1 malignant) and 6 TCCs.
  - Malignant Brenner tumors were negative for p16, Rb, and p53, and strongly positive for Cyclin D1, Ras, and EGFR.
  - TCCs had p53 mutations with p53 and p16 protein overexpression and showed a negative immunoreaction for EGFR, Cyclin D1, and Ras.

- Patient tumor demonstrated p16 and p53 loss and high level EGFR amplification more similar to Brenner tumor than TCCs.

- EGFR overexpression and amplification CLIA validated

- Patient on Cetuximab (08/2011) based on EGFR amplification and the absence of KRAS mutation.
Example 2: Triple Negative Breast Cancer Personalized Genomics Trial

- In collaboration between TGen, Life Technologies and US Oncology and support from Caris Diagnostics, we will sequence the genomes and transcriptomes of tumor and normal tissue from 14 patients with TNBC during the course of clinical management to provide oncologists with additional therapeutic options.

- A subtype of breast cancer that is clinically negative for expression of estrogen and progesterone receptors (ER/PR) and HER2 protein.

- However, there is no effective treatment for chemo-resistant TNBC.
TNBC-001 PTEN Exon 6 homozygous deletion encompassing Exon 6

~1kb PTEN homozygous deletion encompassing Exon 6
Triple Negative Breast Cancer Personalized Genomics Trial

Confidential

Tumor

Exon 5

Exon 6

Exon 7

Normal
PTEN G165Ifs173X protein truncating mutation leads to complete protein loss.

TNBC-001 PTEN Exon 6 homozygous

TNBC-001

Positive Control
Therapeutic Targets on WGS of mTNBC Cancer  TNBC-002

- 58 yo Caucasian transient response preop AC/T, platinum, bevacizumab

- WGS and FISH reveal extrachromosomal DNA BRAF double minute

BRAF oncogene
The clinical effect of the dual-targeting strategy involving PI3K/AKT/mTOR and RAS/MEK/ERK pathways in first-in-human phase I studies: The START Center Experience


START (South Texas Accelerated Research Therapeutics), San Antonio, TX, U.S.A.
CT 2. TNBC with PTEN deletion (AKT inhibitor + MEK inhibitor)

Baseline (03/07/11)  Post 2 Cycles (05/04/11)

PR, 75% regression in primary lesion

Shimizu et al., 2011 (ASCO Abstract 2502)
Messages / Areas of Collaboration

- Multiple high utility events are frequently found in metastatic disease
  - *Not always will be simple black/white in clinic*
- Use of WGS in the context of disease management
- Outcomes and Data Sharing
Thank you