Translational Opportunities from the The Cancer Genome Atlas (TCGA) Project on Muscle Invasive Bladder Cancer

Seth P. Lerner, MD, FACS
Beth and Dave Swalm Chair in Urologic Oncology
Scott Department of Urology
Baylor College of Medicine
Disclosures

• Clinical trials
  – Endo, FKD, Imalux, NCI
• Advisory Board
  – Genentech, Merck, Nucleix, Sitka,
• Consultant
  – Biocancell, Dendreon, Theracoat, Vaxiion
• TCGA – unpaid volunteer
Objectives

• TCGA program overview
• Review some key translatable findings from the TCGA muscle invasive bladder cancer project
• Update integrative analysis
• Opportunities and challenges for translation to the clinic
Group 5: BCRN and Multi-institutional, multi-investigator collaboration: Program Project and Genomics (TT 4 August, 2009)

• Task Force
  – Jessie Au, John Campbell, David DeGraff, Rob Dreicer, Donna Hansel, Seth Lerner, Bill Murphy, Ganesh Raj, Andrew Stephenson, Xi-feng Wu

• Group objectives
  – Establish BCRN-Bladder Cancer Research Network ✔
  – Collaborative multi-platform genomics research project ✔
  – Multi-institutional program project grant ?
<table>
<thead>
<tr>
<th>Data type</th>
<th>Platform</th>
<th>Institution</th>
<th>Team leaders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic mutation – whole exome/ whole genome</td>
<td>Illumina HiSeq SNP 6.0</td>
<td>Broad Institute</td>
<td>Jaegil Kim, David Kwiatkowski, Andy Cherniak, Jonathan Rosenberg</td>
</tr>
<tr>
<td>Copy number variation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA Methylation</td>
<td>Illumina Infinium (HM450)</td>
<td>USC</td>
<td>Peter Laird, Toshi Hinoeu</td>
</tr>
<tr>
<td>mRNA</td>
<td>RNAseq (Illumina HiSeq)</td>
<td>UNC</td>
<td>Katie Hoadley, Billy Kim</td>
</tr>
<tr>
<td>miRNA</td>
<td>RNAseq (Illumina HiSeq)</td>
<td>Univ British Columbia</td>
<td>Andy Mungall, Gordon Robertson</td>
</tr>
<tr>
<td>Protein</td>
<td>RPPA (179)</td>
<td>MDACC</td>
<td>Gordon Mills, Rehan Akbani</td>
</tr>
</tbody>
</table>
TCGA Bladder- What is Next?

- Collect additional clinical and radiologic data
- Clinical outcome correlations
- Functional validation
- Supplemental data 122 pages – lots of data mining
Number of ‘Mutationally Significant’ Genes Identified

- **a)** Number of significant genes vs. number of patients for different tumor types:
  - Bladder
  - Breast
  - GBM
  - AML
  - Endometrial

- **b)** Number of significant genes vs. number of tumor types:

- **c)** Number of significant genes vs. number of patients:

- **d)** Frequency of genes:
  - >20%
  - 10–20%
  - 5–10%
  - 3–5%
  - 2–3%
  - <2%

Significantly mutated genes (n=238)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutated Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>49%</td>
</tr>
<tr>
<td>RB1</td>
<td>17%</td>
</tr>
<tr>
<td>NFE2L2</td>
<td>6%</td>
</tr>
<tr>
<td>FOXA1</td>
<td>5%</td>
</tr>
<tr>
<td>MLL2</td>
<td>27%</td>
</tr>
<tr>
<td>ERCC2</td>
<td>9%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>8%</td>
</tr>
<tr>
<td>PAIP1</td>
<td>5%</td>
</tr>
<tr>
<td>ARID1A</td>
<td>25%</td>
</tr>
<tr>
<td>FGFR3</td>
<td>12%</td>
</tr>
<tr>
<td>TSC1</td>
<td>7%</td>
</tr>
<tr>
<td>BTG2</td>
<td>3%</td>
</tr>
<tr>
<td>KDM6A</td>
<td>24%</td>
</tr>
<tr>
<td>STAG2</td>
<td>14%</td>
</tr>
<tr>
<td>KLF5</td>
<td>6%</td>
</tr>
<tr>
<td>HRAS</td>
<td>4%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>19%</td>
</tr>
<tr>
<td>ERBB3</td>
<td>11%</td>
</tr>
<tr>
<td>TXNIP</td>
<td>7%</td>
</tr>
<tr>
<td>ZFP36L1</td>
<td>7%</td>
</tr>
<tr>
<td>EP300</td>
<td>15%</td>
</tr>
<tr>
<td>FBXW7</td>
<td>8%</td>
</tr>
<tr>
<td>FOXQ1</td>
<td>5%</td>
</tr>
<tr>
<td>RHOA</td>
<td>5%</td>
</tr>
<tr>
<td>ATM</td>
<td>15%</td>
</tr>
<tr>
<td>RXRA</td>
<td>7%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>6%</td>
</tr>
<tr>
<td>CCND3</td>
<td>4%</td>
</tr>
<tr>
<td>CDKN1A</td>
<td>10%</td>
</tr>
<tr>
<td>ELF3</td>
<td>12%</td>
</tr>
<tr>
<td>RHOB</td>
<td>5%</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>2%</td>
</tr>
<tr>
<td>HSP90AA1</td>
<td>7%</td>
</tr>
<tr>
<td>PSIP1</td>
<td>5%</td>
</tr>
<tr>
<td>ZFP36L2</td>
<td>5%</td>
</tr>
<tr>
<td>ZNF513</td>
<td>5%</td>
</tr>
<tr>
<td>PTEN</td>
<td>4%</td>
</tr>
<tr>
<td>CEBPB</td>
<td>2%</td>
</tr>
</tbody>
</table>
Three clusters - mutation/copy number data

Mean and median somatic mutation rate per tumor 7.7 and 5.5 per megabase

- High mutation rate similar to melanoma, lung adeno and Lung squamous cell carcinoma
Three clusters – mutation (n=238)/copy number data

"Focally amplified" Enriched in focal copy number alterations (eg 3p loss/PPARG) and MLL2 mutations
Three clusters – mutation (n=238)/copy number data

Enriched for TP53 and RB1 mutations, E2F3 amplifications

Jaegil Kim, A Cherniack, D Kwiatkowski, J Rosenberg
Three clusters – mutation (n=238)/copy number data

Papillary histology, FGFR3 mutant CDKN2A-deficient

Jaegil Kim, A Cherniack, D Kwiatkowski, J Rosenberg
Integrated Analysis- mRNA, miRNA, RPPA

K. Hoadley
B. Kim
R. Akbani
W. Zhang
Y. Liu
B. Broom
Nature epub 1/29/14
Integrated Analysis- mRNA, miRNA, RPPA

K. Hoadley
B. Kim
R. Akbani
W. Zhang
Y. Liu
B. Broom

Nature epub 1/29/14
Integrated Cluster Analysis

• Cluster III – “Squamous”
  – Enriched with KRT5, 6, 14
  – EGFR
  – Squamous differentiation
  – Similar to “basal” (Chan) and “squamous” (Sjodahl) subtypes

Volkmer…Chan PNAS 2012

Ho, et al Nat Rev Urol 2012
Multiplatform Analysis of 12 Cancer Types Reveals Molecular Classification within and across Tissues of Origin

Cell, epub 8/7/2014
12 Tissue of Origin Sites Translate into 11 COCA Subtypes

COCA – Cluster of Cluster Assignments utilizing 6 platforms: Mutation, copy number, mRNA, miRNA, RPPA, DNA methylation

Chuck Perou, UNC
Integrated subtyping of BLCA distinguishes patient outcomes

- COCA clusters distinguish different survival classes for BLCA
“Approval of a new therapeutic agent in the absence of proven clinical utility or use of a new therapeutic without FDA approval is not permitted. The same should be true for a tumor-biomarker test that is used to guide patient management.”

- 510K clearance does not require clinical utility
The COXEN Principle: Prediction of treatment outcome
(Theodorescu et. al, Proc Natl Acad Sci U S A. 2007;104(32):13086)

**Gene Expression Model**

**Evaluation of Model on Human Tumors**

**Ref:** Clin Can Res 2005;11(7): 2625
**Tx:** Neoadjuvant MVAC (N=45) + surgery or XRT
**Outcome:** Downstaging, Overall survival

**Downstaging vs. COXEN Score**

- **Downstaged**
  - **NO Downstage**

**Downstaging defined as ≤pT1 or ≤T1 after two courses of MVAC**

**P = 0.000656**
**SWOG 1314: A Randomized Phase II Study of COXEN with Neoadjuvant Chemotherapy for Localized Muscle-Invasive Bladder Cancer**

*Impact:* Transform thinking about patient selection for neoadjuvant chemotherapy in urothelial cancer

---

**Activated 7/9/14**

**Tumor Sample TURBT**
- Randomize to chemo $n=184$

**Molecular Analysis**
- Gene expression
- Sequencing
- microRNA
- SNP

**Collection**
- Tissue, blood, urine

**Discovery**

**Cystectomy Pathology**

**Assessment**

To characterize the relationship of MVAC- and GC-specific COXEN scores in terms of pT0 rate

---

**Collection**
- Tissue (>P0), blood, urine

**Molecular Analysis**
- Gene expression
- Sequencing
- microRNA
- SNP

---

Leading cancer research. **Together.**
NCI MATCH
Molecular Analysis for Therapy Choice

• Metastatic disease or locally advanced incurable solid tumors or lymphoma
  – Failed at least one standard therapy

• Co-primary endpoints
  – >25% objective response rate
  – > 35% 6 month PFS

• Screen 3000 patients to get 1000 eligible patients with actionable mutations/amplifications/translocations
Genes that are rarely mutated in one tumor type occur frequently across tumor types

- Alterations in MTOR may also predict sensitivity to everolimus [Wagle et al. Cancer Discovery 2014]
- Low frequency alterations in aggregate and across pathways are even more powerful.

Courtesy Ali Amin-Mansour Broad Institute/TCGA
New baskets looking for PIs
VS6063 / NF2 loss
TDM1 / HER2 amplified
GSK – PTEN loss
MLN0128 / TORC activating or TSC1/2
GSK- AKT 1, 2 mutations
Palbociclib/Trametinib - RAS mutations
Summary

• Delineation of the genomic landscape and molecular subtypes will accelerate biomarker and drug development
• New tools developed for high throughput analysis of NGS data and integrative analysis
• NCI leading in design and support for “basket-type” clinical trials for Phase I/II
Summary

• Cooperative groups developing trials in muscle invasive urothelial bladder cancer for biomarker validation (S1314 COXEN trial) and MATCH-UP (Alliance) in metastatic disease

• CTEP Clinical Trials Planning Meeting proposal for two additional trials in advanced and NMIBC translating TCGA and other genomic project findings