Lung adenocarcinoma genomics

November 28, 2012
TCGA 2nd Annual Symposium
Matthew Meyerson, Ramaswamy Govindan, Steve Baylin, co-chairs
### Key participants in TCGA lung cancer analysis group

#### DNA methylation analysis
- Leslie Cope, Johns Hopkins
- Ludmila Danilova, Johns Hopkins
- Steve Baylin, Johns Hopkins

#### Copy number analysis
- Gad Getz, Broad
- Gordon Saksena, Broad
- Andy Cherniack, Broad

#### Clinical contributors
- Bill Travis, MSKCC
- Dennis Wigle, Mayo Clinic

#### Cross-platform Analysis
- Chad Creighton, Baylor
- Eric Collisson, UCSF
- Sam Ng, UCSC
- Jacob Kaufman, Vanderbilt
- Rileen Sinha, MSKCC
- Ronglai Shen, MSKCC
- Niki Schultz, MSKCC
- Ron Bose, WUSL

#### Biospecimen Core
- Joe Paulauskis, IGC
- Bob Penny, IGC

#### Project management
- Kenna Shaw, NCI
- Laura Dillon, NCI
- Margi Sheth, NCI
- Ram Iyer, NCI
- Brad Ozenberger, NCI

#### Tissue collaborators
- Malcolm Brock, Johns Hopkins
- Ming Tsao, Toronto
- Dennis Wigle, Mayo
- Val Rusch, Memorial Sloan Kettering
- Peter Goldstraw, Royal Brompton
- Kwun Fong, Prince Charles
- Andrew Godwin, Fox Chase
- Maria Raso, MD Anderson
- Rajiv Dhir, Pitt
- Carl Morrison, Roswell Park

#### Working group tri-chairs
- Ramaswamy Govindan, Washington U
- Steve Baylin, Johns Hopkins
- Matthew Meyerson, Dana-Farber/Broad
Lung cancers account for over 25% of cancer deaths in the U.S. each year.

<table>
<thead>
<tr>
<th>Location</th>
<th>Men 292,540</th>
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<td>Lung &amp; bronchus</td>
<td>30%</td>
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<td>Prostate</td>
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<td>Kidney &amp; renal pelvis</td>
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<td>All other sites</td>
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Source: American Cancer Society, 2009.
Lung adenocarcinoma is the most common form of lung cancer

- Lung cancer kills more than 150,000 Americans each year and more than one million people world-wide.
- Major lung cancer histologies are lung adenocarcinoma, squamous cell lung carcinoma, and small cell lung carcinoma.
- Lung adenocarcinoma accounts for ~40% of lung cancer diagnoses and ~65,000 deaths each year in the United States.
- While lung cancer is generally associated with smoking, lung adenocarcinoma uniquely often occurs in non-smokers.
Lung adenocarcinoma: paradigm for molecular subtyping

In recent years, treatments for lung adenocarcinoma have shifted from histology-based strategies to molecular-based strategies.

We have made major advances in treatment for lung adenocarcinoma with targeted inhibitors of EGFR (gefitinib, erlotinib) and ALK (crizotinib) thanks to genomic discoveries.

Example: a patient with lung adenocarcinoma, with a somatic EGFR deletion mutant in exon 19 (thanks to Bruce Johnson, M.D., DFCI)
Weir et al., Nature, 2007: copy number analysis of 371 cases, discovered *NKX2-1* and *TERT* amplifications

Ding, Getz et al., Nature, 2008: mutation analysis of 188 cases, discovered mutations of *NF1, ATM, APC*

Shedden et al., Nat Med, 2008: expression classification of 448 cases

Govindan et al., Cell, 2012: whole genome sequencing of 17 cases, identified smoking/non-smoking signatures

Imielinski, Berger et al., Cell, 2012: whole exome sequencing of 183 cases, identified mutations of *RBM10, U2AF1*

Seo et al., Genome Research, 2012: transcriptome sequencing identified recurrent *MET* splicing alterations
Lung adenocarcinoma therapeutic targets: 2012

Despite the identification of molecular subsets, more than half of all lung adenocarcinomas lack an identifiable driver mutation.

Lung adenocarcinoma drivers

- EGFR
- KRAS
- ALK fusions
- PIK3CA
- AKT1
- MAP2K1
- NRAS
- ROS1 fusions
- KIF5B-RET
- Unknown

Adopted from Pao and Hutchinson, 2012
TCGA lung adenocarcinoma project status

- 303 samples collected
- Adenocarcinoma pathology was confirmed for all cases (W. Travis, MSKCC)
- 230 samples included within the data freeze (10/2/12)
  - Majority of samples excluded were due to pathology review—these cases will be included in a subsequent pan-NSCLC report
- High-quality data across multiple platforms for all samples in freeze
  - Next-gen DNA sequencing, RNA-seq, methylation arrays, proteomic analysis, fusion discovery
- 38 sample pairs with whole genome sequence data (planned)
- First face-to-face meeting tomorrow
- Goal: manuscript submission in February to April, 2013
Copy number analysis of lung adenocarcinoma

- Andrew Cherniack, Broad Institute
- Gad Getz, Broad Institute

- 230 tumor/normal DNA pairs, analyzed on Affymetrix SNP 6.0 arrays
Chromosome arm level copy number in lung adenocarcinoma

Overall Comparison of Copy Number Changes in TCGA Lung Adenocarcinoma and Squamous Cell Carcinoma

LUAD

LUSC

Some differences between LUSC and LUAD.
Focal copy number alterations in lung adenocarcinoma (GISTIC 2.0)

Amplification

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<td>TERC</td>
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Deletion

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<td>CDKN2A</td>
<td>2</td>
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</table>

Andy Cherniack
Exome and RNA sequence analysis of lung adenocarcinoma

- Juliann Chmielecki, Dana-Farber Cancer Institute/Broad Institute
- Mara Rosenberg, Broad Institute
- Matt Wilkerson, University of North Carolina
- Marcin Imielinski, Broad Institute
- Bryan Hernandez, Broad Institute
- Michael Lawrence, Broad Institute
- Neil Hayes, University of North Carolina
- Gad Getz, Broad Institute

- 230 tumor/normal DNA pairs and 230 tumor RNAs, on Illumina paired-end sequencing
Lung adenocarcinoma has a very high rate of somatic mutations
The high mutation rate poses a major problem in identifying significantly mutated genes

- Known recurrently mutated genes (e.g. ERBB2, CTNNB1) do not show up as significant regardless of method used
- Expression filtering enriches for real genes
- However, we need to consider a variety of alternative approaches including…
  - Inclusion of functional significance analysis
  - Two-stage statistical analysis
- In the end, a much larger sample size may be required for elucidation of the full population of lung adenocarcinoma causative mutations
Top 21 mutated genes in lung adenocarcinoma (expression-filtered)

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<th># of patients</th>
<th># of sites</th>
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<td>5</td>
<td>5</td>
<td>6.67E-03</td>
<td>9.66</td>
</tr>
</tbody>
</table>

* candidate novel mutated genes
Intriguing mutated gene candidates in lung adenocarcinoma

- **BCL9L**—homolog, *BCL9*, is translocated in B-cell lymphoma and is reported to encode a protein interacting with beta-catenin.
- **MGA**—reported suppressor of *MYC*, recently reported to be subject to inactivating mutations in B-cell leukemia/lymphoma.
- **MKI67IP**—encodes protein that interacts with Ki-67, encoded by *MKI67*, which is mutated in endometrial cancer.
Correlation of gene mutations among lung adenocarcinoma samples

17  Juliann Chmielecki, Mara Rosenberg

The Cancer Genome Atlas
Recurrent mutations in SWI/SNF chromatin remodeling genes

**ARID1A**


**SMARCA4**

- **p.ATPase** (Potential), **Necessary for interaction with SS18L1/CREST**
- **DEGH box.**

Colors:
- **LXXLL**
- **Silent**
- **Nonsense_Mutation**
- **Missense_Mutation**
- **Frame_Shift_Del**

<table>
<thead>
<tr>
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<td>Missense_Mutation</td>
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<tr>
<td>Red</td>
<td>Frame_Shift_Del</td>
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</table>

**The Cancer Genome Atlas**
Expression-based classification of lung adenocarcinoma

- Matt Wilkerson, University of North Carolina
- Neil Hayes, University of North Carolina
- 230 tumor RNAs, on Illumina paired-end sequencing
Expression clustering of lung adenocarcinoma shows reproducible classes

Matt Wilkerson, Neil Hayes
Expression subtype integrative analysis

- Bronchioid
- Magnoid
- Squamoid

Matt Wilkerson,
Neil Hayes

Gene sequence:
wildtype mutation (mut)

DNA copy number (cn), CIN, deltaN %: -0.3 -0.1 0.1 0.3
expression (expr) & RPPA: -0.75 -0.25 0.25 0.75

n=146
Note other ALK fusions
Are in bronchioid,
Not in 146 group.
Low pass whole genome analysis of lung adenocarcinoma

- Angela Hadjipanayis, Harvard Medical School
- Raju Kucherlapati, Harvard Medical School
- Matt Wilkerson, UNC
- Neil Hayes, UNC

133 tumor/normal DNA pairs for low-pass WGS.
230 tumors for RNA-seq analysis.

Reads were analyzed for structural rearrangements; expression of rearrangements was validated in RNA-seq data.
Fusions identified from RNA-seq involve known fusion partners

- **ALK**
  - TCGA-67-6215 \( EML4\sim ALK \) Bronchioid
  - TCGA-67-6216 \( EML4\sim ALK \) Bronchioid
  - TCGA-78-7163 \( EML4\sim ALK \) Bronchioid

- **ROS1**
  - TCGA-44-2665 \( ROS1\sim CLTC \) Squamoid
  - TCGA-05-4426 \( SLC34A2\sim ROS1 \) Squamoid
  - TCGA-55-6986 \( EZR\sim ROS1 \) Bronchioid
  - TCGA-64-1680 \( CD74\sim ROS1 \) Bronchioid

- **RET**
  - TCGA-55-6543 \( TRIM33\sim RET \) Bronchioid
  - TCGA-75-6203 \(~ RET \) Bronchioid
Recurrent VMP1-RPS6KB1 fusion
t(17;17)(q23.1;q23)

**RPS6KB1**: ribosomal protein S6 kinase, 70kDa, polypeptide 1
**VMP1**: Vacuole Membrane Protein 1

Detected by DNA Sequencing-BreakDancer
7 Tumor Samples/114 RNASeq Samples = ~6.3%
Peptidase fusions in lung adenocarcinoma

**TASP1-RRBP1**

Split Read Detected
2 Tumor Samples/114 RNASeq files

Exon 11 → Exon 12 → Exon 13 → TASP1

Exon 2 → Exon 3 → RRBP1 (5'UTR-promoter)

Peptidase

Rib_recpt_KP: 58
Ribosome_recyc_fac: 322

Overexpression of Peptidase?

**HTRA4-PLEKHA2**

Split Read Detected
2 Tumor Samples/114 RNASeq files

Exon 1 → Exon 2 → Exon 3 → Exon 4 → HTRA4

Exon 9 → Exon 10 → Exon 11 → PLEKHA2

HTRA4: HtrA serine peptidase 4
PLEKHA2: pleckstrin homology domain containing, family A (phosphoinositide binding specific) member 2

Plestrin domain: 7 → 300

Overexpression of Peptidase?
DNA methylation array analysis of lung adenocarcinoma

- Leslie Cope, Johns Hopkins
- Ludmila Danilova, Johns Hopkins
- Steve Baylin, Johns Hopkins

- 181 tumor samples/18 normal DNA pairs, analyzed on Illumina 450K whole genome methylation arrays
**CDKN2A** inactivated by multiple genomic mechanisms in lung adeno

Lung adenocarcinomas frequently lose p16 expression via deletion or methylation.

Compare methylation level in samples where p16 homozygously deleted and methylated. There are around nine thousand significant probes.

- **p16 deleted**
- **tumor**
- **normal**
- **Island**
- **Shore**
- **Shelf**

Brighter blue, higher methylation.
miRNA clustering in lung adenocarcinoma

- Gordon Robertson, BC Cancer Agency
- Andy Chu, BC Cancer Agency

Unsupervised clustering of miRNA sequencing from 352 tumor samples suggested 5 groups.
miRNA clustering in lung adenocarcinoma

miR-10a/183, 143, 375, 148a and 21 discriminate these groups, and are abundant enough that they are likely biologically active.

miR21 defines one large subset of LUAD
Oncogene Negative Analysis

- Alice Berger, Broad Institute
- Eric Collisson, UCSF
- William Lee, MSKCC
- Marc Ladanyi, MSKCC

- Examined mutational events in tumors lacking RTK activation and other “defining” events (e.g. H/N/KRAS, EGFR, ERBB2, BRAF mutation; ALK, RET, ROS fusion negative)
MutSigCV analysis of “oncogene-positive” and “oncogene-negative” sample sets

### Onc pos sample list (n = 139) q < 0.1

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<th>gene</th>
<th>q</th>
<th>rank</th>
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<th>npat (neg)</th>
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Enriched in oncogene positive group

Enriched in oncogene negative group
Integrative cross-platform analysis of lung adenocarcinoma

- Chad Creighton, Baylor
- Eric Collisson, UC San Francisco
- Ron Bose, Washington University
- Niki Schultz, Memorial Sloan-Kettering Cancer Center
- Ted Goldstein, UCSC
- Sam Ng, UCSC
Major deregulation of RTK/RAS/RAF and PI3K/AKT in lung adenocarcinoma
RPPA in lung adenocarcinoma

- Lauren Byers, MD Anderson Cancer Center
- Lixia Diao, MD Anderson Cancer Center
- Gordon Mills, MD Anderson Cancer Center

167 total and phosphorylated proteins quantified by RPPA (reverse phase protein array) in 183 patient tumors.

Tumors cluster into distinct groups that are independent of smoking status.
Lung adeno clusters include RTK activation, MEK activation, and DNA repair groups.
Lung adenocarcinoma: conclusions from TCGA analyses thus far

- Both lung adenocarcinoma and squamous cell lung carcinoma have similar copy number profiles.
- Very high mutation rate—challenge to identify novel mutated genes including MGA.
- Three distinct expression subtypes identified from RNA-sequencing data.
- Multiple fusions are expressed in lung adenocarcinoma.
- Multiple mechanisms for CDKN2A inactivation.
- Distinct miRNA and proteomic clusters.
- Mutational differences between “oncogene positive” and “oncogene negative” subtypes including enrichment of NF1 mutation in oncogene-negative group.
Key participants in TCGA lung cancer analysis group

DNA methylation analysis
Leslie Cope, Johns Hopkins
Ludmila Danilova, Johns Hopkins
Steve Baylin, Johns Hopkins

Gene expression and transcriptome
Neil Hayes, North Carolina
Matt Wilkerson, North Carolina
Gordon Robertson, UBC
Lauren Byers, MD Anderson
Gordon Mills, MD Anderson

DNA sequence analysis
Andrey Sivachenko, Broad
Gad Getz, Broad
Mike Lawrence, Broad

Carrie Sougnez, Broad
Stacey Gabriel, Broad
Eric Lander, Broad
Bryan Hernandez, Broad
Marcin Imielski, Broad
Elena Helman, Broad
Alice Berger, Broad
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