Translation of TCGA data

Lynda Chin, MD
Dana-Farber Cancer Institute
Harvard Medical School
TCGA GBM program: summary

- Defining the atlas of changes in human GBM
  - Deeper insights into known mutations
  - Many novel gene candidates identified
  - Cross-platform validation & interpretation of alterations

- Distinct molecular subtypes of primary GBM defined
  - Potential implication for patient stratification

- New technology for sequencing
  - More data, better data, lower cost…
  - New ways of looking at cancer genomes
Integration and Synergy

Clinical associations
- Environmental exposure
- Histology
- Grade, stage, age
- Survival endpoints
- Treatment responses

Model organisms
- Yeast, flies, worms, fish, mice
- Evolutionary conservation
- Pathways and epistasis
- Biochemical interactions
- Genetic manipulation
- Treatment response
- Tumorigenesis

Human systems
- Cell lines, Xenografts
- siRNAs and cDNAs
- Biochemical interactions
- Molecular mechanisms
- Rx response assessment
- Systems biology
- High throughput screening

Cancer Genome Characterization

Chin and Gray, *Nature*, in press
An example...

**RNAi screen**
- 66 kinases identified be required for cell viability in two GBM cell lines by (Bill Hahn, DFCI/Broad)

**Cancer Genome Data**
- Regions of Amplification in TCGA GBM samples (n=106)

**Developmental Insight**
- 77 genes expressed in SVZ in mouse brain during development (GENSAT Brain Atlas)

5 genes → CDK6
CDK6 and p18\textsuperscript{INK4C} in GBM

- CDK6, not CDK4, is the major CDK that complexes with p16\textsuperscript{INK4A} or p18\textsuperscript{INK4C} on co-IP
- p18\textsuperscript{INK4C} loss-of-function mutants do not bind to CDK6

\textbf{WB: INK4C}

\textbf{IP: CDK6}

\textbf{LN-229: Vector INK4C F37I A61D}

\textbf{WB: INK4C} *

- p18\textsuperscript{INK4C} is a backup tumor suppressor engaged in the relatively common setting of p16\textsuperscript{INK4A} inactivation
  - Loss of p16\textsuperscript{INK4A} $\rightarrow$ enhanced proliferation $\rightarrow$ increased E2F1
  - E2F1 binding to p18\textsuperscript{INK4C} promoter $\rightarrow$ induction of backup

\textit{Wiedemeyer, Brennan, et al, Cancer Cell, in press}
Integration and Triangulation

Clinical associations
- Environmental exposure
- Histology
- Grade, stage, age
- Survival endpoints
- Treatment responses

Model organisms
- Yeast, flies, worms, fish, mice
- Evolutionary conservation
- Pathways and epistasis
- Biochemical interactions
- Genetic manipulation
- Treatment response
- Tumorigenesis

Human systems
- Cell lines, Xenografts
- siRNAs and cDNAs
- Biochemical interactions
- Molecular mechanisms
- Rx response assessment
- Systems biology
- High throughput screening

Cancer Genome Characterization