Vanquishing Cancer Through Genomics

…and by genomics I mean any systematic (genome-wide) approach to define the molecular basis of malignancy and identify curative strategies.
Metaphors of Cancer

- Cancer is a genetic disease
- Cancer is a cell biological disease
- Cancer is an organismal disease
- Cancer is a societal disease
NCI Center for Cancer Genomics: Current Initiatives

TCGA

TARGET

CTD²: A Bridge from Genomics to Cancer Therapeutics
NCI Center for Cancer Genomics: Genomic pipeline

Tissue Source Sites

- Tissue samples & clinical data
- Molecular analytes
- Primary and derived genomic data

Biospecimen Core Resource (BCR)

- Clinical, pathology & tracking data

Genomics Data Commons (GDC)

- Protected & public data

NCI Project Team

- Tracking data
- Primary and derived genomic data

Genome Analysis Network

- Analyzed results

Research Community

RFP to be announced Jan. 2015

RFP to be announced mid 2015
Structural Genomics of Cancer: Two Game Changers

Analysis of formalin-fixed paraffin-embedded biopsies

- Frozen (n=634)
  - 128 (20%)
- FFPE (n=759)
  - 253 (33%)
  - 506

SNV Mutation Discovery

Decreased cost of whole genome sequencing
Define the molecular basis for clinical phenotypes
  - Analyze completed clinical trials of NCI cooperative groups
    - Colorectal cancer
    - Lung adenocarcinoma
    - RFP to be announced to NCTN for genomic analysis of trial samples
  - Alchemist trial in lung adenocarcinoma
  - Exceptional responders initiatives

Define the “full” set of genetic drivers in cancer
  - Pilot projects in colorectal, lung adeno, and ovarian cancer

Next generation cancer models for functional genomics

Develop NCI Genomics Data Commons (GDC)
Jean Claude Zenklusen, Ph.D.
Director
TCGA Program Office
National Cancer Institute
Case Accrual and Analysis Status

TCGA Tumor Project Progress as of November 2014

- Manuscript submitted or published
- Analysis underway
- Cancelled
- Not started
- Rare tumor project

Number of Cases Shipped (Final)

BRCA  OV  UCEC  KIRC  GBM  HNSC  LUAD  LGG  LUSC  THCA  SKCM  COAD  STAD  BLCA  LAML  READ  KICH  PRAD  LUC  CESC  KIRP  SARC  PAAD  ESCA  PCPG  UVM  ACC  UES  CHOL  TGCT  THYM  MESO  DLBC
TCGA Gastric Cancer Project – The Power of Integrative Analysis
TCGA Gastric Cancer Project – The Power of Integrative Analysis

- **CIN**
  - Intestinal Tumors
  - TP53 Mutation
  - RTK-RAS Activation

- **EBV**
  - PIK3CA Mutation
  - PD-L1/2 Overexpression
  - EBV-CIMP
  - CDKN2A Silencing
  - Immune Cell Signaling

- **GS**
  - Diffuse Tumors
  - CDH1, RHOA Mutations
  - CLDN18-ARHGAP Fusion
  - Cell Adhesion

- **MSI**
  - Hypermethylation
  - Gastric-CIMP
  - MLH1 Silencing
  - Mitotic Pathways
Histopathology of Gliomas

Low grade gliomas

Astrocytoma

Oligodendroglioma

Glioblastoma Multiforme
Survival With Glioblastoma Multiforme vs. Low Grade Glioma

Low grade gliomas
Glioblastoma multiforme
Common Genetic Profiles in Glioblastoma and a Subset of Low Grade Gliomas

- **Low grade gliomas**
  - IDH mutant
    - 1p/19q co-deletion
  - IDH mutant
    - 1p/19q WT

- **Glioblastoma**
  - IDH wild type
  - IDH wild type

**Genes**: TP53, RB1, PTEN, PIK3R, PIK3C, PIK3C2, PDGFRA, NF1, MET, MDM4, MDM2, MDM1, IDH1, FGFR3, FGFR2, FGFR1, EGFR, CDKN2C, CDKN2A, CDK6, CDK4, BRAF, ATRX
Daniela Gerhard, Ph.D.
Director
Office of Cancer Genomics
National Cancer Institute
The Ph-like subtype of B cell Acute Lymphoblastic Leukemia
## Kinase Fusions Discovered in Ph-like ALL

<table>
<thead>
<tr>
<th>Kinase Gene</th>
<th>Tyrosine Kinase Inhibitor</th>
<th>Fusion Partners</th>
<th>Patients number</th>
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<tr>
<td>ABL1</td>
<td>Dasatinib</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>ABL2</td>
<td>Dasatinib</td>
<td>3</td>
<td>7</td>
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<td>JAK2 inhibitor</td>
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<td>JAK2 inhibitor</td>
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<td>19</td>
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<td>IL2RB</td>
<td>JAK1 inhibitor, JAK3 inhibitor, or both</td>
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<td>NTRK3</td>
<td>Crizotinib</td>
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<tr>
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<tr>
<td>TYK2</td>
<td>TYK2 inhibitor</td>
<td>1</td>
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</tr>
</tbody>
</table>
Response of Pediatric B-ALL With a EBF1-PDGFRB Translocation to Imatinib

- 10 year old male with refractory B-ALL – 70% blasts at day 29
- Cytogenetics: 5q alteration => interstitial deletion by array CGH disrupting EBF1 and PDGFRB genes
- $EBF1$-$PDGFRB$ fusion translocation detected by RT-PCR

- Commenced imatinib
- Immediate clinical improvement
- 1 week: morphological remission
- 2 weeks: MRD 0.017%
- Consolidation chemotherapy added

$=>$ Patient remains in CR > 2 years

Identification and Treatment of Ph-Like ALL

Identify Ph-like ALL by LDA Card

Candidate testing
Fusions: RT-PCR
*CRLF2* alterations: FISH/PCR
JAK/IL7RA/SH2B3 mutation

Kinome Capture and RNA-seq
If candidate screens negative

WGS
If above negative

**ABL1/ ABL2/ PDGRFB/ CSF1R fusion positive:**
Add dasatinib in prospective phase and compare outcome to that of pts from retrospective phase
Important Open Questions in Cancer Structural Genomics

What is the molecular basis of clinical phenotypes?
   Aggressive vs. indolent disease
   Metastatic vs. localized disease
   Response to therapy
   Mechanisms of resistance
Important Open Questions in Cancer Structural Genomics

What is the molecular basis for cure vs. relapse following adjuvant chemotherapy?

Opportunities in colorectal cancer and lung adenocarcinoma
Disease-free Survival in Stage 2-3 Colorectal Cancer Treated with Adjuvant FOLFOX Chemotherapy

~25% cure
~75% relapse

Is there a molecular basis for this clinical difference?

% Alive and disease-free

Years

NSABP C-08
Influence of Tumor Genetics on Progression-free Survival in Colorectal Cancer Treated With Adjuvant Chemotherapy

Ras-MAPK pathway

KRAS/BRAF WT

KRAS mutant

BRAF mutant

P-value = 0.0142

Sinicrope et al. Gastroenterology 2014, in press
Opportunity: Completed NCI Adjuvant Trials in Colorectal Ca

Question: Can tumor genomics at diagnosis predict outcome to adjuvant therapy?

Plan: Whole exome/genome sequencing + transcriptome sequencing
- Compared equal #s of biopsies from cured vs. relapsed cases
- Identify genetic or gene expression predictors of survival
- Use training and test set paradigm to validate predictor

Promise: A molecular predictor could reduce the frequency/duration of surveillance
=> Decreased anxiety for patient and decreased healthcare costs
Benefit of Adjuvant Chemotherapy in Stage 1-3 Non-small Cell Lung Carcinoma

Hazard ratio = 0.84
P-value = <0.001

Surgery alone
Surgery + chemoRx

~60% relapse
~40% cure

Is there a molecular basis for this clinical difference?

Opportunity: Completed NCI Adjuvant Trial in NSCLC

ECOG 1505 (~1000 adenocarcinoma biopsy samples)

Eligible: N = 1500
Resected (R0) IB (≥ 4 cm)-IIIA
≥ Lobectomy
No previous chemotherapy
No planned radiation therapy

Stratified:
- Stage (IB (≥ 4 cm), II, IIIA-N2, IIIA-T3N1
- Histology (squamous vs. other)
- Sex
- Chemotherapy regimen*

Randomize

Chemotherapy × 4 cycles
Chemotherapy × 4 cycles plus Bevacizumab × 1 year
Overall survival primary endpoint

Question: Can tumor genomics at diagnosis predict outcome to adjuvant therapy?

Plan: Whole exome/genome sequencing + transcriptome sequencing
Compared equal #s of biopsies from cured vs. relapsed cases
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Promise: A molecular predictor could reduce the frequency/duration of surveillance
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Important Open Questions in Cancer Structural Genomics

- What is the “full” extent of genetic drivers in cancer?
  - Can we define genetic events occurring in >2% of patients?
  - Which genetic events co-occur and which are mutually exclusive?  => Define genetic pathways to cancer
  - Will whole genome sequencing discover non-coding driver mutations and cryptic chromosomal rearrangements?
The Mutational Burden of Human Cancer

Childhood cancers

Carcinogens

Increasing genomic complexity

Mike Lawrence and Gaddy Getz
Many Cancer Drivers With <20% Prevalence Remain Undiscovered
Driver Genes in Lung Adenocarcinoma

- NKBR2 amp (2.2%)
- RIT1 (2.2%)
- MET amp (2.2%)
- None
- NF1
- 8.3%
- 24.4%
- 32.2%
- KRAS

Genes:
- HRAS (0.4%)
- NRAS (0.4%)
- RET fusion (0.9%)
- MAP2K1 (0.9%)
- ALK fusion (1.3%)
- ROS1 fusion (1.7%)
- ERBB2 (1.7%)
- MET ex14
- 4.3%
- 7.0%
- 2.2%
- 11.3%

Drugs:
- Neratinib
- Tivantinib
- Vandetanib
- Cabozantinib
- Crizotinib
- LDK378
- Neratinib
- Tivantinib
- Vemurafenib
- Erlotinib
- Afatinib
- Gefitinib

TCGA Nature 2014
Crizotinib Produces Prolonged Objective Responses in Lung Adenocarcinoma with ROS1 translocation

Shaw et al. NEJM 371:1965 (2014)
Driver Genes in Lung Adenocarcinoma

- ERBB2 amp: 24.4%
- MET amp: 8.3%
- RIT1: 2.2%
- None: 32.2%
- KRAS: 11.3%
- EGFR: 7.0%
- BRAF: 4.3%
- MET ex14: 0.9%
- ALK fusion: 1.3%
- ROS1 fusion: 1.7%
- ERBB2: 1.7%
- MAP2K1: 0.9%
- NRAS: 0.4%
- HRAS: 0.4%

TCGA Nature 2014
Power Calculation for Cancer Driver Discovery

Lawrence et al, Nature 2014
Discovery of Cancer Drivers With 2% Prevalence

Lawrence et al, Nature 2014
Cancer Driver Discovery Cohort

- TCGA
- Completed clinical trials
  - NCI-sponsored
  - Institutional
- Prospective clinical trials
  (e.g. Alchemist)
- Existing institutional cancer biopsy banks
Prospects in Cancer Functional Genomics

Computational Genomics

Functional Genomics
Integration of Functional Genomics and Structural Genomics is Required to Identify Essential Cancer Pathways

Structural genomics

- Cancer biopsy
- Copy number
- Rearrangements
- Sequence

Functional genomics

- RNAi
- CRISPR
- Small molecules
- Mutant ORFs

Develop relevant cancer model

Putative driver genes
Modeling the Diversity of Human Cancer: An Unmet Need

- Genetic analysis has identified recurrent genetic lesions in cancer that range in frequency from 1% - >50% of cases.
- Most cancer cell lines have not been directly compared to the primary tumor using current genomic methods.
- Existing cell line models of common cancer types are suspect biologically and genetically (e.g. prostate CA).
- Models of rare cancer subtypes may be nonexistent or underrepresented.
- Models do not exist for many recurrent genetic lesions in human cancer, and for common combinations of lesions.
- Existing models do not recapitulate hierarchical relationships of tumor subpopulations (i.e. tumor propagating cells, stroma).
Next Generation Models of Epithelial Cancers

Organoid cultures

Clevers laboratory
Sato et al. Gastroenterology 2011 141:1762
Using Next Generation Cancer Models to Develop Therapies

Engelman lab
Crystal et al. Science 2014, in press
Using Next Generation Cancer Models to Develop Therapies

Combo drug screen with Gefitinib

Engelman lab
Crystal et al. Science 2014, in press
A Next Generation Cancer Model Network

Site 1

Site 2

Site 3

Human Cancer Models

Genomic data

Wide distribution to cancer researchers
Goals for Cancer Computational Genomics
IOM Report on Precision Medicine Envisioned a Knowledge Network of Disease
Development of the NCI Genomics Data Commons (GDC) To Foster the Molecular Diagnosis and Treatment of Cancer

Bob Grossman PI
Univ. of Chicago
Leidos

Knowledge Network

Target Identification
Marker Identification
Molecular Mechanisms
Biomedical Research

Taxonomic Classification

Treatment
Diagnosis
Health Outcomes

Validation

Informed Mechanistic Studies

Basic Sciences Discovery

Molecular Characterization
Electronic Health Records

Clinical Discovery

Observational Studies During Normal Course of Clinical Care
NCI Genomics Data Commons (GDC) Functionality

1. Import and standardize genomic and clinical data from legacy programs
2. Harmonize mapping of sequence data to the genome / transcriptome
3. Implement state-of-art methods for derived data:  
   • mutation calls  
   • copy number  
   • structural variants  
   • digital gene expression
4. Maintain data security and manage authorized access
5. Provide data for download or computation on a co-localized compute cluster
6. Open GDC for upload of new genomic data for comparison with existing data and shared access
Utility of a Cancer Knowledge System

- Identify low-frequency cancer drivers
- Define genomic determinants of response to therapy
- Compose clinical trial cohorts sharing targeted genetic lesions

Cancer information donor
Questions?