Realizing society’s expectations of the cancer community
Realizing society’s expectations of the cancer community

Anna Barker: Intro

1. Stuart Schreiber: Overview and small-molecule probes
2. William Hahn: LoF, GoF RNA
3. Andrea Califano: Systems analyses
“Towards patient-based cancer therapeutics” Andrea Califano, Daniela S. Gerhard, William C. Hahn, Scott Powers, Michael Roth, Stuart L. Schreiber, in review
Relating a genetic feature of a cancer to the efficacy of a drug

Philadelphia translocation: Janet Rowley

- **Imatinib**
- Matched small-molecule therapy
- Chemotherapy
- No treatment

**Graph Details:**
- **Overall survival (%)**
- **Months after beginning treatment** (Kaplan-Meier survival curve)

**Citation:**
Can these type of dependencies, reflected by cancer genotype/drug efficacy relationships, be discovered comprehensively?
Facilitate efficient paths for clinical development *prospectively*

Patient populations, biomarkers, drug targets and resistance mechanisms are identified concurrently and from the outset.

Relate the genetic features of cancers to acquired cancer dependencies and identify small molecules that target the dependencies (1Broad; 2CSHL; 3Columbia; 4DFCI; 5UTSW)
Relate the genetic features of cancers to acquired cancer dependencies and identify small molecules that target the dependencies (1Broad; 2CSHL; 3Columbia; 4DFCI; 5UTSW)
Small-molecule cancer probes against challenging targets

- Growth, differentiation, survival factors
- Membrane receptors
- Transcription factors
  - Sonic Hedgehog, HB-EGF
  - DDR1
  - GPCRs, kinases, etc.
  - NFkB, GATA1, Myc, C/EBPα, HOXA13;
    HDAC6, JMJD2C

(targets of small molecules whose functions have been modulated in cells)
Advances exploited by CTD² and enabling a disciplined approach to cancer drug discovery:

• innovations in **next-generation synthetic chemistry** that reach ‘undruggable’ targets or processes.

• innovations in cell culturing and screening in physiologically relevant conditions (**tumor microenvironment**)

• innovations in determining the targets and **mechanisms** of small-molecule probes and drugs.
Relate the genetic features of cancers to acquired cancer dependencies and identify small molecules that target the dependencies (1Broad; 2CSHL; 3Columbia; 4DFCI; 5UTSW)
Small-molecule probes of ID4: an ovarian cancer oncogene

Loss-of-Function: Genes essential for ovarian cancer proliferation

Gain-of-Function: Genes that induce ovarian tumor formation

Cancer Genome Annotation: Cross reference with genes in amplified regions in OvCa (TCGA)

Bill Hahn et al.
Small-molecule probes of ID4: an ovarian cancer oncogene

**Loss-of-Function** Genes essential for ovarian cancer proliferation

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**Cancer Genome Annotation** Cross reference with genes in amplified regions in OvCa (TCGA)

ID4 SM probe development

1536-well plate

Bill Hahn et al.
Relate the genetic features of cancers to acquired cancer dependencies and identify small molecules that target the dependencies (1Broad; 2CSHL; 3Columbia; 4DFCI; 5UTSW)
Small-molecule probes of STAT3 in glioblastoma multiforme

Andrea Califano et al.
Small-molecule probes of STAT3 in glioblastoma multiforme

GBM patient

master regulator module(s)

STAT3 SM probe development

1536-well plate

Andrea Califano et al.
CTD² Network: challenging probe development projects

<table>
<thead>
<tr>
<th>Assay Project Name</th>
<th>Collaborator</th>
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<tbody>
<tr>
<td>Stat3 - SMM</td>
<td>Columbia-CTD²</td>
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<td>CEBPβ/δ - SMM</td>
<td>Columbia-CTD²</td>
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<td>DFCI-CTD²</td>
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<td>tumor cell dependency</td>
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<td>Myc</td>
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<td>JARID1A</td>
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<td>Glut1</td>
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<td>Deubiquitinase</td>
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</table>
Relate the genetic features of cancers to acquired cancer dependencies and identify small molecules that target the dependencies (¹Broad; ²CSHL; ³Columbia; ⁴DFCI; ⁵UTSW)
Modeling human cancers: cancer genetic features in mice

A context-specific functional genetic screening platform: promoting cancers

Scott Lowe, Scott Powers, et al.; and Ron DePinho, Linda Chin, Bill Hahn
Modeling drug target inhibition: inducible RNA \textit{in vivo}

Scott Lowe, Scott Powers, et al.

- Transplantable cancer models for target identification (screens) and validation
- Germ-line transgenic mice for functional studies and assessment of potential drug toxicities

A context-specific functional genetic screening platform: \textbf{eliminating cancers}

Scott Lowe, Scott Powers, et al.
Targeting non-oncogene co-dependencies (synthetic lethality)

- Target oncogene (e.g., BCR-ABL/imatinib, muEGFR/erlotinib)

- Target ‘non-oncogene co-dependency’ (e.g., for muRAS: 1) hexokinase and 2) GSTP1/CBR1/AHNAK)

- Stress inducers (paclitaxel, irinotecan): cytotoxics

Stockwell, Haggarty, SLS, Chem & Biol, 6, 71-83 (1999);
see also: Luo, Solimini, Elledge, Cell, 136, 823-37 (2009)
RAS changes cancer metabolism and small-molecule sensitivity

Arvind Ramanathan, SLS (2005)
Drugs matched to genetic features, **not** cancer metabolism

- **RAS**
  - 2-deoxyglucose
    - Ramanathan & Schreiber PNAS, 2005
  - glucose transporter
    - Yun et al. Science 2009

- **aerobic glycolysis**
  - glutamine transporter
    - Wise et al. PNAS 2008
  - glutaminase
  - MYC
    - oligomycin; glutamine depletion
      - W. G. Kaelin & C. B. Thompson, Nature 2010
  - AKT
    - 2-deoxyglucose
      - Fan et al. J Biol. Chem. 2010

- Glutamine transporter
  - Fan et al. J Biol. Chem. 2010

- Glutaminase
  - Wise et al. PNAS 2008
RAS changes ROS biology and small-molecule sensitivity

- Discovered in an NCI ICG probe project
- Induces cell death/apoptosis in transformed but not in normal cells
- Prevents tumor growth *in vivo* (xenograft and spontaneous cancer models) in low doses safely
- Quantitative proteomics reveals a target: GSTP1/CBR1/AHNAK complex, and mechanism-of-action studies reveal a process: dissipation of ROS

“Sensing the cancer genotype by targeting stress response to ROS results in selective killing of cancer cells by a small molecule”, submitted
Sensitivity to BRD293 is conferred by mutant RAS

Mutant RAS increases levels of ROS in cells: Lee et al., *J. Biol. Chem.* **274**, 7936-7940 (1999)
CTD<sup>2</sup> probe development for additional targets in ROS biology

Cancer drugs matched to genetic features, not ‘ROS metabolism’
Cell-line models of cancer: from NCI-60 to ChemBank

**NCI-60:** Cancer cell line/small molecule sensitivity relationships ($GI_{50}$ measurements)

**NCI-sponsored ChemBank:** Cancer cell line/small molecule sensitivity/cell measurement relationships (Paul Clemons)
Next-generation cancer cell line databases: CTD\textsuperscript{2} at UTSW

- Lung cancer genotypes (examples from 8 clades)
- Global RNAi and 250,000 small molecules
- Cancer cell measurement
- Relationships between biological objects/states
- Relationships between small molecules
- Roles of quantitative variables

See also studies at MGH (Settleman, Haber & collaborators)
HTS identifies selective small-molecule vulnerabilities in NSCLC
Cancer cell line encyclopedia: a promising public resource

**CCLE** 1,000 genomically characterized cancer cell lines:
- copy number (Affy SNP 6.0 array)
- gene expression (U133 + 2 array)
- mutation profiling (OncoMap v3):
  - Total target genes: 1,645
  - Total exons: 25,261

Diagram: Cancer cell line distribution by type:
- NSCLC
- colorectal
- breast
- pancreas
- prostate
- liver
- ovarian
- lymphoma
- SCLC
- bone; osteosarcoma; leukemia T-ALL; CML; medulloblastoma; neuroblastoma; fibrosarcoma
- leukemia B-All
- lymphoma (H)
- lymphoma (NH_T)
- thyroid; CLL
- endometrial
- AML; melanoma
- gastric
- head & neck
- glioma
- kidney
- bladder
- esophageal
- ovarian
- lymphoma
- liver

Broad/Novartis CCLE Project: Jordi Barretina, Levi Garraway, Bill Sellers, and collaborators
CTD² probe kit: highly **specific** SM probes of new cancer targets

225 ‘narrowly active’ probes and growing; **36%** are accessed by **complete synthesis**

- Target
- MOA
- Selectivity
- Potency
- Structure
- Clinical Status

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Ben Munoz, Aly Shamji and the CTD² team
**CTD² probe kit representative examples; a living collection**

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<tr>
<th>Compound</th>
<th>Pathways</th>
<th>Target/Depend</th>
<th>Potency</th>
<th>Selective</th>
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reported in past several months
CCLE and the CTD$^2$ small-molecule probe kit (in progress)

1,000 CCLs (genetic features)

CTD$^2$ probe kit (high specificity)

relationships between biological objects/states

relationships between small molecules

cancer cell measurement

relationships between cell measurements

8 (in duplicate) concentrations

roles of quantitative variables
CTD² pilot of the probe set suggests new clinical directions

CTNNB1 activating mutation

BCL2 antagonist ABT 263

subset of 1,000 cancer cell lines

IC50 (μM)
CTD² pilot of the probe set suggests new therapeutics (HDAC6)

VHL loss-of-function mutation

subset of 1,000 cancer cell lines
CTD\textsuperscript{2} is discovering and using small-molecule probes of cancer

Discover small-molecule probes that target non-traditional cancer dependencies (TFs; chromatin; etc.)

Discover relationships between cancer genetic features and small-molecule efficacies

BRD293

RNA LoF/GoF; systems analyses

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Small-molecule probes
CTD² Network: an integrated approach to cancer therapeutics
CTD² pilot of the probe set suggests new therapeutics

**KRAS status**
- wt
- mut

**EC50 (uM)**
- 150nM
- 20uM

**% viability**
- 10 colon lines

3/5 wt resistant
4/5 mut sensitive

indisulam
BRD-6043