Over 100 Cell Types Susceptible to Cancer, Each With Multiple Molecular Etiologies
Current Cancer Drug Development

<table>
<thead>
<tr>
<th></th>
<th>Oncology compounds</th>
<th>All compounds</th>
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<tr>
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<tr>
<td>Preclinical testing</td>
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<td>Phase I</td>
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<tr>
<td>Approval</td>
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...at an average cost of $1B per drug

adapted from: Sharpless and DePinho; Nature Reviews Drug Discovery ‘06
Over 100 Cell Types Susceptible to Cancer, Each With Multiple Molecular Etiologies
Multiple GEM Modeled on Human Cancer Genetics/Biology

- glioma medullo rhabdoid epithelial...
- pancreatic stomach GIST
colon HCC ...
- lymphomas Leukemias Myelomas
- osteosarcoma mets
- sarcomas
- melanoma carcinomas
- breast ovarian endometrial
- kidney bladder prostate
- head & neck
- NSCLC SCLC mets
- prostate
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GEM in Clinical Translation

- Cancer genome
- Cancer transcriptome
- Cancer proteome
- Serum proteome

frequent aberrations

cancer patient

engineer programmed aberrations

cancer initiation and progression

GEM model

gene, transcriptome proteome, metabolome disease-relevant “fingerprints” biomarker discovery target discovery target validation pre- + co-clinical trials
NSCLC: A Paradigm for Tailoring Cancer Management


KRAS mut, erloti + chemo

Ding et al., *Nature 2008*

Eberhard et al, *JCO '05*
Cancer is a Dynamic and Evolutionary Process

adapted from Hanahan and Weinberg, Cell 2000
GEM in Clinical Translation

Cancer genome
Cancer transcriptome
Cancer proteome
Serum proteome

frequent aberrations

engineer programmed aberrations

cancer patient

cancer initiation and progression

GEM model

genome, transcriptome, proteome, metabolome disease-relevant “fingerprints” biomarker discovery
target discovery target validation pre- + co-clinical trials
Inducible GEM NSCLC Reflects Human Treatment Response

**EGFR**$^{L858R}$

6 days on Erlotinib

**EGFR**$^{\Delta L747-S752}$

2 weeks on Erlotinib

**Kras**$^{G12D}$

4 weeks on Erlotinib

Politi et al (Varmus) G&D 2005
Preclinical Assessment Guides Clinical Trial

L858R

- Before treatment
- 1-wk treatment

Ji et al, (Wong) Cancer Cell 2006

Clinical trial HKI272
Acquired Resistance of Human EGFR-NSCLC to Inhibitors

- Unknown (40%)
- T790M (40%)
- MET Amplification (10%)
- T790M + MET Amplification (10%)
Preclinical Assessment Guides Combination Therapy Clinical Trial

Resistant Double EGFR Mutant

**erlotinib**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Relative Tumor Volume</th>
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<tr>
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<tr>
<td>1</td>
<td>1</td>
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<tr>
<td>2</td>
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**rapamycin**

<table>
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</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
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**HKI 272**

<table>
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<tr>
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</tr>
<tr>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
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**HKI272+CCI-779**

**Rapamycin & HKI272**

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</table>
Preclinical Assessment Predicts Combination Therapy Effective in Ras-driven NSCLC

K-Ras driven NSCLC
MEK (ARRY) and/or PI3K/mTor (BEZ) inhibitor

Ding et al., Nature 2008

Engelman et al, (Wong)
Nature Medicine 2008
Multiple GEM Modeled on Human Cancer Genetics/Biology
Inducible Mouse Lung Cancer Models

- KRAS G12D
- KRAS G12V
- KRAS G12C
- EGFR Del19
- EGFR L858R
- EGFR T790M
- EGFR wild type
- EGFR vIII
- HER2 exon 20 insertion
- HER2 wild type
- BRAF V600E
- ELM4-ALK
- IGF1R
- C-MET
- EGFR T790M-Del19/c-MET
- EGFR T790M-L858R/c-MET
- EGFR T790M-Del19
- EGFR T790M-L858R
- EGFR Del19/IGF1R
- EGFR L858R/IGF1R
- p110 exon 20 (H1047R)
- ROS1
- ELM4-ALK
- IGFR
- C-MET
- EGFR T790M-Del19/c-MET
- EGFR T790M-L858R/c-MET
- EGFR T790M-Del19
- EGFR T790M-L858R
- EGFR Del19/IGF1R
- EGFR L858R/IGF1R
- p110 exon 20 (H1047R)
- ROS1
- ELM4-ALK
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<th>Research Area</th>
<th>Example</th>
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<tr>
<td>Identification of novel genes involved in carcinogenesis</td>
<td>Nedd9 involvement in metastatic progression of melanomas</td>
<td>Kim, et al., Cell 2006</td>
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<tr>
<td>Determination of predictive molecular signatures for various cancer types</td>
<td>Kras-associated expression signatures in lung carcinogenesis</td>
<td>Sweet-Cordero, et al., Nature Genetics, 2005</td>
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<td>Discovery of novel early tumor prognostic markers</td>
<td>A compendium of circulating early markers for pancreatic cancer</td>
<td>Harsha, et al., PLoS Medicine, 2009</td>
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<td>Analysis of pathway dynamics in disease via systems biology approaches</td>
<td>Analysis of prion disease progression through systems approach</td>
<td>Hwang, et al., Mol Syst Biology, 2009</td>
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<tr>
<td>Genetics</td>
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<td>Astro/variable</td>
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<td>$kRas; Akt; Ink4a/Arf^{−/−}$</td>
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Adapted from Huse and Holland (2009) Br. Path.