The Need for Urgent Reform in the Organization and Funding of Cancer Research and Clinical Trials

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Arizona State University  
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Declared Interests:

- Board of Directors: Monsanto, Exelixis, Caris Life Sciences
- Scientific Advisory Board: Synthetic Genomics, Anacor
- IOM Forum on Global Infectious Diseases
- USG Activities: DoD, DHS
Key Themes

Defining the Causal Molecular Pathologies in Human Cancer: Identification of ‘Driver’ versus ‘Passenger’ Perturbations

Implications of the Extravagant Scale of Molecular Pathway Perturbations in Cancer for Future Drug Discovery and Clinical Care

Investment in New Diagnostic Technologies to Detect Early (Pre-Metastatic) Diseases Will Provide Better Returns Than The Search for Novel Therapeutics

Silos Subvert Solutions: The Imperative for Major Changes in the Organization and Funding of Cancer Research and Clinical Trials to Better Integrate Discovery and Clinical Care
“The War on Cancer”

National Cancer Act of 1971
December 23, 1971

Science (2011) 331, 1539

Celebrating an Anniversary

In this issue of Science, we commemorate the 40th anniversary of the U.S. National Cancer Act, which provided a massive stimulus for cancer research. At the start of this “Cancer Crusade,” researchers were already tackling some tough questions, as reflected in papers published by Science in 1971. Among them: How do abnormalities in chromosome number arise in tumor cells? Can tissue-specific markers be used to determine the epithelial versus mesenchymal origin of a solid tumor? Can the immune system be manipulated so that it recog-
Challenge Goal

“To eliminate suffering and death due to cancer by 2015”

Dr. A. C. von Eschenbach
Director, National Cancer Institute
2003
<table>
<thead>
<tr>
<th>Site</th>
<th># People (thousands)</th>
<th>% change</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>2010</td>
<td>2020</td>
</tr>
<tr>
<td>Breast</td>
<td>3461</td>
<td>4538</td>
</tr>
<tr>
<td>Prostate</td>
<td>2311</td>
<td>3265</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1216</td>
<td>1517</td>
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<tr>
<td>Melanoma</td>
<td>1225</td>
<td>1714</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>639</td>
<td>812</td>
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<tr>
<td>Uterus</td>
<td>588</td>
<td>672</td>
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<tr>
<td>Bladder</td>
<td>514</td>
<td>629</td>
</tr>
<tr>
<td>Lung</td>
<td>374</td>
<td>457</td>
</tr>
<tr>
<td>Kidney</td>
<td>308</td>
<td>426</td>
</tr>
<tr>
<td>Leukemia</td>
<td>263</td>
<td>240</td>
</tr>
<tr>
<td>All Sites</td>
<td>13,772</td>
<td>18,071</td>
</tr>
</tbody>
</table>

Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

Genomics

Proteomics

Molecular Pathways and Networks

Network Regulatory Mechanisms

ID of Causal Relationships Between Network Perturbations and Disease

Patient-Specific Signatures of Disease or Predisposition to Disease
Classification of Six Subgroups of Medulloblastoma

From Pharmaceuticals to Pharmasuitables: Right Rx for the Right Disease (Subtype)

ID Molecular Targets for Rx Action

Disease Profiling to Identify Subtypes (+ or - Rx Target)
### Subtypes of Melanoma

S. J. Vidwans et al. (2011) PLoS ONE

#### III. The Melanoma Disease Model

Latest version of III. The Melanoma Disease Model online at Cancer Commons ([http://mmdm.cancercommons.org](http://mmdm.cancercommons.org))

<table>
<thead>
<tr>
<th>Detailed sub-types</th>
<th>Pathway(s)</th>
<th>Key gene/biomarker(s)</th>
<th>Diagnostic technologies</th>
<th>Potentially relevant therapeutics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>MAPK</td>
<td>BRAF</td>
<td>Targeted sequencing</td>
<td>BRAF inhibitors</td>
</tr>
<tr>
<td>1.2-1.3</td>
<td>BRAF/PTEN</td>
<td></td>
<td>Targeted sequencing &amp; IHC</td>
<td>(BRAF inhibitors) AND (PI3K inhibitors, AKT inhibitors or mTOR inhibitors)</td>
</tr>
<tr>
<td>1.4</td>
<td>BRAF/AKT</td>
<td></td>
<td>Targeted sequencing &amp; Copy number</td>
<td>(BRAF inhibitors) AND (AKT inhibitors or mTOR inhibitors)</td>
</tr>
<tr>
<td></td>
<td>BRAF/CDK4</td>
<td></td>
<td>Targeted sequencing &amp; Copy number/CGH</td>
<td>(BRAF inhibitors) AND (CDK inhibitors)</td>
</tr>
<tr>
<td>2.1</td>
<td>c-KIT</td>
<td>c-KIT</td>
<td>Targeted sequencing</td>
<td>Gleevec &amp; other inhibitors</td>
</tr>
<tr>
<td>3.1</td>
<td>GNAQ</td>
<td>GNAQ</td>
<td>Targeted sequencing</td>
<td>MEK inhibitors</td>
</tr>
<tr>
<td>3.2</td>
<td>GNA11</td>
<td></td>
<td>Targeted sequencing</td>
<td>MEK inhibitors</td>
</tr>
<tr>
<td>4.1</td>
<td>NRAS</td>
<td>NRAS</td>
<td>Targeted sequencing</td>
<td>MAPK &amp; PI3K pathway inhibitors; Farnesyl transferase inhibitors</td>
</tr>
<tr>
<td>5.1</td>
<td>MITF</td>
<td>MITF</td>
<td>Copy number</td>
<td>HDAC inhibitors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Detailed sub-types</th>
<th>Pathway(s)</th>
<th>Key gene/biomarker(s)</th>
<th>Diagnostic technologies</th>
<th>Potentially relevant therapeutics</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1</td>
<td>AKT/PI3K</td>
<td>PTEN</td>
<td>IHC</td>
<td>PI3K inhibitors, AKT inhibitors or mTOR inhibitors</td>
</tr>
<tr>
<td>6.2</td>
<td>AKT</td>
<td></td>
<td>Copy number</td>
<td>AKT inhibitors, mTOR inhibitors</td>
</tr>
<tr>
<td>6.3</td>
<td>PI3K</td>
<td></td>
<td>IHC</td>
<td>PI3K inhibitors, AKT inhibitors or mTOR inhibitors</td>
</tr>
<tr>
<td>7.1</td>
<td>CDK</td>
<td>CDKN2A</td>
<td>Targeted sequencing / CGH</td>
<td>CDK inhibitors or HDAC inhibitors</td>
</tr>
<tr>
<td>7.2</td>
<td>CDK4</td>
<td></td>
<td>Copy number / CGH</td>
<td>CDK inhibitors or HDAC inhibitors</td>
</tr>
<tr>
<td>7.3</td>
<td>CCDN1/Cyclin D</td>
<td>Copy number / CGH</td>
<td></td>
<td>CDK inhibitors or HDAC inhibitors</td>
</tr>
<tr>
<td>8.1</td>
<td>P53/BCL</td>
<td>Bcl-2</td>
<td>IHC</td>
<td>TBD</td>
</tr>
<tr>
<td>8.2</td>
<td>p53</td>
<td></td>
<td>Targeted sequencing</td>
<td>TBD</td>
</tr>
<tr>
<td>9</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
</tr>
</tbody>
</table>
K-RAS Profiling and Anti-EGFR Monoclonal Antibody Therapy

- higher response in patients with K-RAS versus mutant-K-RAS
- estimated $604 million/year savings (ASCO)

clinical guidelines

- regulatory endorsement in product labeling
Molecular Medicine and Rational Therapeutics: Molecular Diagnostics and Targeted Rx

- opening era in linking disease molecular pathology to rational Rx
- increasing payor, regulatory and public pressures for reliable ID of Rx-responsive patients
- demand for Dx-Rx combinations will intensify
- Dx-Rx combination will become an obligate element of NDA/BLA submission and product labeling
- development of Dx-Rx combinations as intrinsic components of R&D programs for investigational Rx

Companion Therapeutics Selected by Precision Diagnostics
“The problem with all these tests, soon I’ll have nothing I can offer my patients”

Molecular Profiling and Segmentation of Patient Populations: New Clinical Trial Designs to Reduce Time, Cost and Failure Rates in Anti-Cancer Drug Development
Molecular Profiling and Segmentation of Patient Populations and New Clinical Trial Designs

- rationale that only patients with the relevant Rx molecular target(s) will respond
  - streamline drug development via enrichment trials in target-positive patient subsets

- key assumptions
  - molecular target(s) selected predict/correlate with Rx efficacy
  - robust assay available (regulatory complexities of validation/qualification)

- logistical and economic issues in ID of small/rare target-positive patient subsets
  - size of initial screening cohort
  - need for multi-center consortia (national/international)
Large Scale Profiling of Cancer Patients to Identify Cohorts Expressing Rx Target(s) for Phase II Trials

<table>
<thead>
<tr>
<th>Target</th>
<th># Patients Screened</th>
<th># Eligible Patients</th>
<th># Centers</th>
<th># Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML4 ALK⁺: lung cancer*</td>
<td>1500</td>
<td>82</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>HER2⁺: gastric cancer**</td>
<td>3803</td>
<td>549</td>
<td>122</td>
<td>24</td>
</tr>
</tbody>
</table>

* E.L. Kwak et al. (2010) NEJM 363, 1693
** Y. Bang et al. (2010) Lancet 376, 687
How Should the Value of Oncology Drugs Be Assessed?
# The Continued Price Escalation for New Cancer Therapies

<table>
<thead>
<tr>
<th>Therapeutics</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendreon</td>
<td>$93,000</td>
</tr>
<tr>
<td>PROVENGE (sipuleucel-T)</td>
<td>$120,000</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>$144,000</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>$???,000 (million dollars for some melanoma patients?)</td>
</tr>
<tr>
<td>PROLEUKIN (aldesleukin)</td>
<td>$???,000 (million dollars for some melanoma patients?)</td>
</tr>
</tbody>
</table>

T. Turnham, Exec. Director, Melanoma Research Foundation. The Pink Sheet. 11 April 2011
Hurdles for Regulatory Approval and Clinical Adoption of Cancer Treatments

“The bar for what we call ‘significant’ has fallen so low we risk tripping over it.”

Dr. Antonio Tito Fojo
Head, Experimental Therapeutics Section, NCI.
2010 AACR Meeting cited in Oncology Times 25June 2010
Pivotal Phase III Studies Used for FDA Approval of Targeted Anti-Cancer Drugs

**Tarceva (erlotinib): Genentech**
- 2005 approval for use with gemcitabine for pancreatic cancer
- increased median survival by 10 days

**Vectibix (panitumumab): Amgen**
- 2006 approval for advanced CRC
- tumor progression slowed by 5 days
<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Study</th>
<th>Bevacizumab Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PFS (months)</td>
</tr>
<tr>
<td>Breast</td>
<td>ECOG E2100</td>
<td>+5.9*</td>
</tr>
<tr>
<td></td>
<td>AVADO</td>
<td>+0.8*</td>
</tr>
<tr>
<td></td>
<td>RIBBON-1</td>
<td>+2.9*</td>
</tr>
<tr>
<td>Ovarian</td>
<td>GOG 0218</td>
<td>+0.9</td>
</tr>
<tr>
<td>Lung</td>
<td>ECOG E4599</td>
<td>+1.7*</td>
</tr>
<tr>
<td>Gastric</td>
<td>AVAGAST</td>
<td>+1.4*</td>
</tr>
<tr>
<td>Pancreas</td>
<td>CALGB 80303</td>
<td>+0.9</td>
</tr>
<tr>
<td>CRC</td>
<td>Hurwitz</td>
<td>+4.4*</td>
</tr>
<tr>
<td></td>
<td>Saltz</td>
<td>+1.4</td>
</tr>
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</table>

*Statistically significant

NICE Gets Nasty (or Rational?)
Value-Based Insurance Designs (V-BID)

- section 2713(c) of Patient Protection and Affordable Care Act
- WHO guidance on value of life threshold for cost effectiveness should be 300% of GDP per capita
  - US = $140,000 ($11,600/month)
The Cost of Cancer Care: The Example of Addition of Bevacizumab to Standard Therapy

- **GOG Study 218 (J. Clin. Oncol. 2011 29, 1247)**
  - $401,088/progression-free life year saved

  - over $200,000/QALY

- **AVADO, RIBBON1 and ATHENA studies (J. Clin. Oncol. 2011 29, 1222)**
  - no cost estimate but median PFS lower than in ECOG E2100

- **NICE (UK) estimated QALY of $170,000 to $400,000**
What Are We Willing to Pay for Added Months of Survival in Cancer?

<table>
<thead>
<tr>
<th>Lifetime cost above standard care</th>
<th>If cancer is on par with other diseases ($150,000 per life year gained), months of added overall survival benefit needed</th>
<th>Treating cancer as worthy of much higher reimbursement ($250,000 per life year gained), months of added overall survival benefit needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>$50,000</td>
<td>4 months</td>
<td>2.4 months</td>
</tr>
<tr>
<td>$100,000</td>
<td>8 months</td>
<td>4.8 months</td>
</tr>
<tr>
<td>$150,000</td>
<td>12 months</td>
<td>7.2 months</td>
</tr>
<tr>
<td>$200,000</td>
<td>16 months</td>
<td>9.6 months</td>
</tr>
<tr>
<td>$250,000</td>
<td>20 months</td>
<td>12 months</td>
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<td>$300,000</td>
<td>24 months</td>
<td>14.4 months</td>
</tr>
<tr>
<td>$350,000</td>
<td>28 months</td>
<td>16.8 months</td>
</tr>
<tr>
<td>$400,000</td>
<td>32 months</td>
<td>19.2 months</td>
</tr>
<tr>
<td>$450,000</td>
<td>36 months</td>
<td>21.6 months</td>
</tr>
<tr>
<td>$500,000</td>
<td>40 months</td>
<td>24 months</td>
</tr>
</tbody>
</table>

Source: Pink Sheet 13 Sept. 2010. Adapted from S. Ramsey FHCRC, ASCO 2010
How Many Drugs Acting on the Same Target Can The Market Support?  
PI3K Inhibitors in Cancer Clinical Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Status</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayer</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>Exelixis/Sanofi</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>Genentech/Roche</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>Novartis</td>
<td>Phase I/II</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>Novartis</td>
<td>Phase I/II</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>Semafore</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>Exelixis/Sanofi</td>
<td>Phase I/II</td>
<td>PI3K</td>
</tr>
<tr>
<td>Genentech/Roche</td>
<td>Phase I</td>
<td>PI3K</td>
</tr>
<tr>
<td>Novartis</td>
<td>Phase I/II</td>
<td>PI3K</td>
</tr>
<tr>
<td>Oncothyreon</td>
<td>Phase I/II</td>
<td>PI3K</td>
</tr>
<tr>
<td>Zenyaku Kogyo</td>
<td>Phase I</td>
<td>PI3K</td>
</tr>
<tr>
<td>Novartis</td>
<td>Phase I</td>
<td>PI3Kα</td>
</tr>
<tr>
<td>Amgen</td>
<td>Phase I</td>
<td>PI3Kδ</td>
</tr>
<tr>
<td>Calistoga Pharma</td>
<td>Phase I/II</td>
<td>PI3Kδ</td>
</tr>
<tr>
<td>Genentech/Roche</td>
<td>Phase I</td>
<td>PI3Kα</td>
</tr>
</tbody>
</table>

SOURCES: Semafore, ClinicalTrials.gov
“The system for conducting cancer clinical trials in the US is approaching a state of crisis. …if the clinical trials system does not improve its efficiency and effectiveness, the introduction of new treatments will be delayed, and patient lives will be lost unnecessarily”

A National Cancer Clinical Trials System for the 21st Century
Reinvigorating the NCI Cooperative Group Program
National Academies Press, Washington, DC
When Will We Achieve a Framework for Rational, Quality Cancer Care

- multiple IOM reports but little change happens
  - Ensuring Quality Cancer Care (1999)
  - To Err is Human (2000)
  - Crossing the Quality Chasm (2001)
- slow evolution of Professional Society Treatment Guidelines and even slower adoption by community oncologists
- standard-of-care largely uninfluenced by new MDx approaches to profile patients for optimum Rx selection
- less than 5% US cancer patients enrolled in investigational Rx trials and community oncologists ill-formed about investigational options
The Distressing State of Investigational Cancer Drug Trials in the USA

- Sateren et al. 2002 J. Clin. Oncol. 20, 2109
  - less than 5% US cancer patients enrolled in trials
- Durivage et al. 2009 J. Clin. Oncol. 27, 337s
  - 2685 industry and NCCN trials at 14 cancer centers
  - 1455 (54.2%) failed to accrue a single patient
- Dilts et al. 2009 J. Clin. Oncol. 27, 1761
  - 296 to 481 steps to activate trials by NCI-STEP and/or cooperative groups
- lag to launch NSCLC trials longer than median/patient survival time
- initiation of EC/Asia trials x2 faster than in USA
- increasing offshore migration of clinical trials
randomized controlled trials (RCT) accorded status as highest for evidentiary value/regulatory approval

survey of 262 RCTs 2005-2008 revealed 20-30% lack critical data for replication
  - JNCI (2010) 102, 702

what constitutes a ‘positive trial’ in oncology?: defining the magnitude of clinical benefit
  - prespecified in Phase III investigational protocol

review of 18 RCTs for drug approved since 2000
  - only 4 met or exceeded pre-specified endpoints
  - JNCI (2011) 103, 16
Adequacy of Published Oncology RCTs to Provide Therapeutic Details Needed for Clinical Utility

(J.M. Duff et al. 2010 JNCI 102, 702)

- ten essential parameters regarding dosing and regimen
- only 30 of 339 studies (11%) fulfilled all ten
- failure to meet Consolidated Standards of Reporting Trials (CONSORT) guidelines
- failure of journals to reinforce compliance
  - space limitations and volume of supplemental data
- need for improved open access to trial protocols
Clinical Trials of New Cancer Drugs

- complex clinical, statistical and regulatory issues in selection of appropriate ‘endpoints’
  - PFS, TTP, SPP and OS
- improved TTP and PFS do not necessarily lead to improved OS
- use of OS as endpoint
  - additional trial size for sufficient statistical power
  - cost and speed of trials, cost of care
Challenging the Dogma of Current Guidelines and Standard(s) of Care (SOC)
The Case for Access to Expanded Treatment Options for Cancer Patients

- most SOC regimens still compromised by significant refractory disease
  - intrinsic and acquired resistance
- SOC as major obstacle to evaluation of new investigational agents/novel combinations
- evaluation of new agents/combinations on treatment failure patients is conceptually flawed
  - tumor cell phenotypes in ‘last resort’ patients may have little or no resemblance of tumor cell populations at initial detection
Medical Ethics and Difficult Questions for Oncologists

• first, do no harm!

   but

• does SOC treatment with high cost/high toxicity drugs without evidence that the relevant Rx target(s) is expressed represent a harm? (or just ignorance and laziness?)

• does failure (or overt refusal) to make patients aware of MDx profiling as an option to guide their Rx selection constitute a harm? (and legal liability?)

• Rx without MDx is analogous to treating patients with HIV or other microorganisms with known high frequency of Rx-resistance without profiling the organism’s resistance/susceptibility
Why Are Cancer Drug Discovery and Effective Therapy So Difficult?
Surging Investments in Oncology R&D*

- 861 oncology/cancer drugs in clinical trials
- 147 equity offerings
- 30 debt offerings
- 117 partnerships
- 81 licensing agreements
- 4 PE deals
- 158 VC deals

*2010 data: [http://edbgroup.com-globaldatareport](http://edbgroup.com-globaldatareport)
*PhRMA: website accessed Feb.2011
Imatinib Mesylate (Gleevec®)

• initial approval (2001) for CML
  – treatment response and dose optimization via assay of BCR-ABL kinase inhibition in mononuclear blood cells from patients
• additional inhibition of oncogene C-KIT and expansion of therapeutic utility to GIST
  – C-KIT exon 11 mutations increased sensitivity
  – exon 9 mutations less sensitive
  – GISTs lacking C-KIT mutations or alternative receptor kinase PDGFRA exhibit low responses
Understanding Disease at the Molecular Level: Mapping Pathway Perturbations

Network Pharmacology and Drug Discovery: Key Principles

- there are few single molecular targets for Rx action
- effective Rx requires modulation of pathways
- there are no linear pathways, only networks and subnetworks
- there are also highly interconnected networks/subnetworks between tissues
  - e.g. modulation of liver network induces changes in pancreatic islet network
The Evolution of Drug Discovery

- empirical screening

- cellular and molecular pharmacology but continued reliance on whole cell assays reproduced significant level of ‘systems-complexity’

- genomics and HTS of isolated molecular targets: reductionism and elimination of systems complexity/context

- mapping molecular pathways and networks and a return to systems pharmacology
The Challenge of Drug Discovery in Late-Onset, Chronic, Multigenic Diseases

- mapping complex alterations in multiple molecular pathways and subnetworks particularly in chronic, progressive disease
  - separation of driver versus passenger perturbations for Rx action

- ID of pathway/subnetwork connectivities, cross-talk and redundancies and implications for Rx strategies for “homeostatic reset”
  - multi-target Rx action

- designing suitable polypharmacology for multiple Rx targets
  - SAR promiscuity in a single molecule
  - Rx combinations
  - limit adverse off-target effects and/or on-target binding in non-target tissues
The Challenge of Drug Discovery for Late-Onset, Chronic, Multigenic Diseases

- complexity and multiplicity of pathway/network perturbations increases the probability of Rx refractoriness/resistance via compensatory pathways
- amplified pathway and subnetwork perturbations with disease progression?
  - significant inter-patient and intra-patient heterogeneity
  - cancer as the most extreme example?
The Complexity of Cancer Genomes

LUNG CANCER
Cancer: small-cell lung carcinoma

- Sequenced: full genome
- Source: NCI-H209 cell line
- Point mutations: 22,910
- Point mutations in gene regions: 134
- Genomic rearrangements: 58
- Copy-number changes: 334

Highlights:
Duplication of the CHD7 gene confirmed in two other small-cell lung carcinoma cell lines.

SKIN CANCER
Cancer: metastatic melanoma

- Sequenced: full genome
- Source: COLO-829 cell line
- Point mutations: 33,345
- Point mutations in gene regions: 292
- Genomic rearrangements: 51
- Copy-number changes: 41

Highlights:
Patterns of mutation reflect damage by ultraviolet light.

BREAST CANCER
Cancer: basal-like breast cancer

- Sequenced: full genome
- Source: primary tumour, brain metastasis, and tumours transplanted into mice
- Point mutations: 27,173 in primary, 51,710 in metastasis and 109,078 in transplant
- Point mutations in gene regions: 200 in primary, 225 in metastasis, 328 in transplant
- Genomic rearrangements: 34
- Copy-number changes: 155 in primary, 101 in metastasis, 97 in transplant

Highlights:
The CTNNB1 gene encodes a putative suppressor of metastasis that is deleted in all tumour samples.

BRAIN CANCER
Cancer: glioblastoma multiforme

- Sequenced: exome (no complete Circos plot)
- Source: 7 patient tumours, 15 tumours transplanted into mice (follow-up sequencing on 21 genes for 83 additional samples)
- Genes containing at least one protein-altering mutation: 685
- Genes containing at least one protein-altering point mutation: 644
- Copy-number changes: 281

Highlight:
Mutations in the active site of IDH1 have been found in 12% of patients.
Tumor-Stroma Interactions in Cancer Progression

- Growing recognition as factor in tumor aggressiveness and Rx responsiveness
- Genetic analysis of micro-dissected tumor-associated stroma
- Poor prognosis associated with high expression of hypoxia and angiogenesis genes
- Low expression of type 1 immune response genes
- Release of paracrine survival (anti-apoptosis) factors by stromal cells
- Elevated stromal ‘metagene’ expression profile correlates with poor response to anthracycline-based neoadjuvant therapy in human breast cancer
- Role of tumor cell epithelial-to-mesenchymal transition (EMT) and exosomes in modulating stromal response?
Cancer Therapeutics: The Most Perplexing Question of All

- Is the scale of perturbations in multiple pathways and subnetworks in metastatic, advanced disease in the solid malignancies an insurmountable technical barrier to design of poly-target (promiscuous) agents and/or Rx combinations needed to achieve curative or even effective therapy?

- Is the only viable strategy for major progress in reducing the profound clinical, economic and emotional toll of cancer to focus on early diagnosis and removal of pre-metastatic lesions?
Successful Use of MDx for Early (Pre-Metastatic) Detection in Major Cancers Will Not Eliminate Need for New Rx and Rational Rx Selection Tools

- **solid malignancies**
  - fraction of patients will still present with advanced disease due to failure to use new MDx detection platforms

- **hematopoietic malignancies**
  - distributed nature of malignant cells precludes surgical excision
  - valuable role of MDx in subtyping patients for presence/absence of Rx target(s)
Rethinking Approaches to Cancer

Is There a Fundamental Imbalance in Investment in Diagnostics Versus Therapeutics?
Biomarkers, Biosignatures and Molecular Diagnostics: Key Value Drivers in Reducing The Impact of Cancer
The Poor Performance Record of Biomarker Discovery and Validation

- ‘publish and vanish’
  - over 120,000 claimed biomarkers or biomarker combinations (biosignatures)
  - less than 100 molecular diagnostics in clinical use or advanced validation trials
- literature dominated by anecdotal studies
  - academic laboratories
  - lack of standardization: biospecimens to analytical platforms
  - small patient cohorts and insufficient statistical power
  - poor replication and confirmatory studies
- widespread lack of understanding of regulatory requirements in academic research community
  - GLP, GMP, Records, RUO instruments versus Clinical Use
  - technical complexities of multiplex assays
  - new regulatory oversight (IVDMIAs)
Identification and Validation of Disease-Associated Biomarkers: Obligate Need for a Systems-Based Approaches

- Standardized Biospecimens and Molecular Pathway Analysis
- Multiplex Biomarker Validation and Complex Signal Deconvolution
- New Instrumentation, and Automated Analytics
- Clinical Impact and Patient Monitoring
Building Large Scale, Standardized Resources for Biomedical Research

- rigorously phenotyped/matched/consented disease and normal specimens
- biobanking: leadership and national policies to create a vital research resource
- standardization of pre-analytical and analytical methods
- standardized data ontologies and formats for large scale datasets/federated databanks
“The technological capacity exists to produce low-quality data from low-quality analytes with unprecedented efficacy.”

“We now have the ability to get the wrong answers with unprecedented speed.”

Dr. Carolyn C. Compton
Director, Office of Biorepositories and Biospecimen Research
National Institutes of Health
‘I0M, July 2010’
“We may be lost, but we’re having a good time”

Yogi Berra
Access to High Quality Biospecimens, Biobanks and DNA Repositories: A Major Obstacle for Biomarker Discovery
Time Between Ligation Of Main Artery And Tumor Resection (Intrasurgical Ischemia) Affects Gene Expression In Colon Cancer (NCI-Indivumed study)

Intrasurgical Ischemia

PCA mapping: grouping of warm ischemia time points

Indivumed-NCI Study: Courtesy of Dr. C. C. Compton
Access to Quality Biospecimens for Medical Research: A Critical ‘Choke Point’ in Biomedical Research

Ease of Acquiring the Quality of Biospecimens

Question Their Data Because of the Quality of Biospecimens

Limit Research Scope of Work Due to the Shortage of Quality Biospecimens

http://biospecimens.cancer.gov/cahub/
Blood-Based Multiplex Diagnostics

- blood as highly informative biospecimen for Dx profiling
- bathes all organs
- many ‘biosignatures’ from diseased tissues expressed in blood
- minimally invasive, low cost acquisition and ease of repeated sampling versus tissue biopsy
- each patient acts as their own control for longitudinal monitoring

Source: For the Record 12-6-10
“The study of cancer cells in two dimensions seems quaint if not archaic”


“Medline search reveals that more than 80% of cancer and molecular biologists still use two-dimensional techniques”

D.W. Hutmacher (2010) Nature Materials 9, 90
Challenging Questions

- are the phenotypes and molecular pathways of cell lines and 2D cell cultures so unrepresentative of the situation to render them irrelevant and pose blind avenues for diagnostic/therapeutic discovery?

- can the biology of metastasis be elucidated by analysis of non-metastatic cells?
A Global Map of Human Gene Expression

- 5372 microarray samples
- 206 different laboratories
- 163 different laboratories
- 369 ‘groups’
  - cell or tissues type, disease state or cell line
- PCA gene expression matrix of 14,000 genes X 5372
- cell lines cluster together rather than with their claimed tissues of origin
  - 1217 up regulated genes
  - cell division/mitosis genes
- fresh cancer samples cluster as intermediate group between homologous normal tissue and immortalized cell lines

A global map of human gene expression
http://www.ebi.ac.uk/gxa/array/U133A
Automated Annotation of Cell Morphology

Characterize each patient sample using quantitative morphological features

H&E Stained Breast Cancer Microscopic Image  Labeled Tissue Regions
Segmented Cells and Nuclei  Labeled Subcellular Regions
Validation of Disease Associated Biomarkers: Scale and Statistical Power

- the high dimensionality small sample size (HDSS) problem
  - high number of variables (2000-10000) and low sample size (10-100)
  - increased risk of selection of variables due to chance (overfitting)
- disease related differences are small compared to biological variability
- many variables behave as QTLs with graded continuum rather than binary normal: disease separation
- statistical powering of validation studies
  - “the 20:200:2000 rule”
Whole Genome Sequencing (WGS)

- rapid improvements in instrumentation, cost and speed
- higher information content than exome profiling
- combination with transcriptome profiling to ID chimeric fusion transcripts
- cost:performance trajectory for WGS may soon be cheaper than cumulative cost from expanding panels of individual MDx tests
- eliminates IP challenge/royalty mountain issue with multiplex MDx panels
Big Genomics and Managing Massive Data

- sequence data generation outstripping analytics
- 1000 Genomes Project (2010) generated more data in 6 months than GenBank accumulated in 21 years
- NGS storage as high-resolution images imposes disproportionate archiving burden
  - shift to discard raw data and easier to resequence samples (assumes availability)
- data analytics and bioinformatics personnel as major choke points for large scale population profiling studies
- customized data conversion for different decision categories and decision-makers
- causal correlations with disease and Rx responsiveness established by metanalysis of large WGS datasets will shift many clinical sequencing needs back to specific genomic regions
Adoption of New Technologies in Healthcare

- not merely innovation in technology
- parallel evolution and adoption of new business, financial and organizational models
- complexity of harmonizing incentives for diverse constituencies
- critical role of public policies in defining market entry barriers
  - regulation, reimbursement
  - professional standards and sustaining status quo
  - administrative procedures
  - governance of third party health insurance payments
- cost-based, event-/procedure-based incentives versus integrated care/disease management
Social Networks and Consumer: Patient Empowerment

POWER TO THE PATIENT

Source: R&D Directions May 2010
Physician Reported Barriers to Use of Patient Decision Assists (pDAs) in Oncology

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Surgeon &lt;50% cancer</th>
<th>Surgeon &gt;50% cancer</th>
<th>Speciality in Center Medical Oncologists</th>
<th>Speciality in Center Radiation Oncologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of awareness</td>
<td>81%</td>
<td>71%</td>
<td>52%</td>
<td>50%</td>
</tr>
<tr>
<td>No resources</td>
<td>17%</td>
<td>37%</td>
<td>42%</td>
<td>36%</td>
</tr>
<tr>
<td>Deemed Nnt relevant or value not established</td>
<td>17%</td>
<td>24%</td>
<td>46%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Adapted from: C. Brace et al. (2010) J. Clin. Oncol. 28, 2286
The Production, Diffusion and Consumption of Information and Knowledge: An Increasingly Complex Ecosystem

- Massive Data
- Data Standards and Inter-operable Federated Databanks
- Increasing Importance of Open Source Systems
- New Organizational Networks, Funding Policies and Infrastructure Investment
Mining The Data Deluge:

- nomenclature ontologies
- liberate intelligence from multiple source formats
- interoperability challenges
- early discovery (chaos) vs. clinical trials (CDISC) vs. healthcare (HL7, SNOMED)
- urgent imperative for methodological, ontological and data storage format standards
Open Sources and New Knowledge Networks for Efficient Use and ROI on Research Investments

Keynote: Alyssa Goodman, Harvard – Robertson Auditorium
“Seamless Astronomy: How astronomers share, explore and discover”

Cover, (Apr 5, 2011) PNAS
Open Data Systems and Crowd Sourcing in Biomedical R&D
the potential economic and health benefits from biosignature diagnostic profiling transcend any other current category of innovation in cancer

realization of this objective will require radical changes in the organization and funding of research and clinical trials

three parameters: specimens, scale and standards are fundamental to achieving tangible progress in comprehending cancer pathogenesis, improved diagnosis and rational Rx selection
realization of this potential will depend not only on technological advances but equally on circumvention of entrenched cultural, institutional and economic interests in sustaining the status quo

moving from silos to systems
The Most Important Barriers to Change in Biomedical Research

- cultural
  - silos subvert solutions
  - protection of the status quo
  - reward structures
- funding
  - not just dollars
  - imperative for new systems-based organizational and operational approaches to address complex multidimensional problems
- education and training
  - single discipline focus and perceived career path rewards
  - anachronistic P&T criteria
- leadership gaps in defining coherent national policies for research and healthcare delivery
THE PROMISE OF TRANSLATIONAL MEDICINE

With Francis Collins now calling the shots at NIH, will he be able to deliver on the innovations behind the genome?
Coordination of the Complex Interactions Required to Build a Productive Translational Medical Research Capacity

- reform current CTSA funding to require systems-based assembly of full expertise spectrum and obligate industry participation
- promulgation of standards and centralized orchestration of resources (national/international)
  - biorepositories and biospecimens
  - ‘omics’ analytics reference standards
  - informatics standards and infrastructure support (BIX, HIX)
- incentives
  - public:private partnerships and consortia
  - value-based reimbursement
- proactive regulatory science
  - advanced diagnostics
  - standards for metadata and outcomes research
- enlightened policies for preventive care
  - reimbursement for annual physical and multiplex Dx
New Diagnostic Technologies as Key Value Drivers for Improved Disease Detection and Clinical Care

- Predictive
- Preventive
- Personalized
- Participative

- Precision diagnostics
- Better care and improved outcomes at lower cost
- Optimized treatment decisions
- Health status monitoring

Politics

Price