Cancer Genetics and Epigenetics: Growing Impact on Cancer Medicine

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- Movement toward Personalization of Cancer Care
- Genetic/Epigenetic Biomarkers as Resource Allocation Tools
Mapping/Sequencing of the Human Genome

- Milestone in molecular biology
- Revolutionized cancer genetics and epidemiology
  - New technologies for molecular profiling of cancer cells
  - Unprecedented opportunities for the discovery of new approaches to cancer treatment and prevention
  - Greatly augmented public expectations
  - Increased cancer care costs?
## Transformation of Medicine by Translational Research*

<table>
<thead>
<tr>
<th>20th century medicine</th>
<th>21st century medicine</th>
<th>implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>treat disease when symptoms arise and normal function is compromised</td>
<td>intervene before symptoms appear and preserve normal function</td>
<td>prevention of disease and preservation of health</td>
</tr>
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<td>morphological understanding of disease state</td>
<td>cellular/molecular understanding of evolving disease process</td>
<td>prediction of disease risk permitting less toxic and more effective intervention</td>
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<tr>
<td>high financial and disability costs</td>
<td>opportunity for improved efficacy and efficiency</td>
<td>personalization of risks and treatments; greater participation of patients in health care decision-making</td>
</tr>
</tbody>
</table>

*adapted from Hood L, von Eschenbach A, and Zerhouni E (2005-6)
Current Challenges of Drug Discovery and Development

Flow of Approved Products*

- Lead Identification
- Chemistry
- Lead Optimization
- Pharmacologic
- Candidate Selection
- Production & Formulation
- Safety Assessment
- Phase I Clinical Trials
- Phase II Clinical Trials
- Phase III Clinical Trials
- Approval by U.S. Food and Drug Administration

*Barker A, National Cancer Institute; PhRMA (www.phrma.org)
Current Challenges of Drug Discovery and Development

Flow of Approved Products*

861 drugs in clinical trials for cancer in 2009
(122 for lung ca, 107 for breast ca, 70 for colorectal ca, 103 for prostate ca)

1-2 new drugs approved for cancer each year

devlopment costs >$1B/drug

devlopment time >10 years

approval by U.S. Food and Drug Administration

*Barker A, National Cancer Institute; PhRMA (www.phrma.org)
The Discovery and Development of Anti-Cancer Drugs: Role of “Translational Research”*


- target/pathway discovery
- target “credentialing”
- drug discovery (identification of leads; lead optimization)
- preclinical drug development (safety/toxicity; manufacturing)
- Investigational New Drug (IND) application filed with Food and Drug Administration

coordinated development of biomarkers for risk stratification and pharmacodynamics
Historical Development Pathway for Anti-Cancer Drugs

Investigational New Drug (IND) application filed with Food and Drug Administration

Phase 1 (Toxicity) Testing
Goal is to determine the dose and dose-schedule for the drug
(MTD = maximally tolerated dose; DLT = dose-limiting toxicity)

Phase 2 (Efficacy) Testing
Goal is to estimate/define drug benefit
(Response rates: complete responses + partial responses)

Phase 3 (Comparative Efficacy)
Goal is to test patient benefit

FDA Approval/Labeling for Marketing
New Development Pathway for Anti-Cancer Drugs

Investigational New Drug (IND) application filed with Food and Drug Administration

Phase 1/2 (Toxicity/Efficacy) Testing
Goals are: (i) to determine optimal biological dose (the dose that maximizes “on-target” effects while minimizing “off-target” effects, using molecular biomarker of pharmacodynamic action),

and (ii) to estimate drug benefit in setting with maximal chance of efficacy (using molecular biomarker of risk/for indication)

Phase 3 (Comparative Efficacy)
Goal is to test patient benefit

FDA Approval/Labeling for Marketing
Imatinib (Gleevec®): “Targeted” Therapy for Chronic Myelogenous Leukemia (CML) and Gastrointestinal Stromal Tumors (GISTs)
Imatinib binds to inactive Bcr-Abl (not phosphorylated at Tyr-393) and distorts N-terminal region of activation loop, freezing enzyme into an inactive conformation.

Bcr-Abl kinase domain showing activation loop. During catalysis, the N-terminal region of the activation loop adopts an open conformation to bind magnesium and coordinate phosphate groups of ATP; the C-terminal region binds substrates.

**Imatinib Efficacy in Chronic Myelogenous Leukemia (CML)**

Hematologic response to imatinib in *Bcr-Abl* chronic myelogenous leukemia (CML)

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>All Patients</th>
<th>Patients with Responses</th>
<th>Patients with Complete Responses</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>no. (%)</td>
<td></td>
</tr>
<tr>
<td>25 or 50</td>
<td>6</td>
<td>2 (33)</td>
<td>0</td>
</tr>
<tr>
<td>85</td>
<td>4</td>
<td>2 (50)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>140</td>
<td>3</td>
<td>3 (100)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>200 or 250</td>
<td>16</td>
<td>16 (100)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>300–1000</td>
<td>54</td>
<td>54 (100)</td>
<td>53 (98)</td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>77 (93)</td>
<td>64 (77)</td>
</tr>
</tbody>
</table>

High Dimensional Sequencing of Cancer Genomes Reveals Both Common and Rare Gene Defects in Human Cancers*

New Technologies Detect Cancer-Specific Gene Mutations in Blood and Body Fluids
Opportunity for Screening and Early Detection*

“BEAMing” for mutant DNA

DNA Methylation Patterns in Normal Cells Versus Cancer Cells

DNA Methylation Biomarkers Improve Lung Cancer Staging*

stage 1 non-small cell lung cancer (no spread to mediastinal lymph nodes)

MGMT CpG Island/Promoter Methylation and Glioblastoma Response to Temozolomide*

Pharmacogenetics of Tamoxifen for Breast Cancer
Improved Efficacy, Improved Safety, Cost Savings*

*Goetz MP et al. J Clin Oncol 23: 9312- (2005);
Trends in DNA sequencing…
Impact of New Technologies*

*Service RF Science
311: 1544-6 (2006)

2007: $10^{-4}$/bp

2008: $10^{-5}$/bp

2009: $10^{-6}$/bp

*Hutchison CA Nucl Acids Res
35: 6227-37 (2007)

... and still going ...
Cancer Genetics and Epigenetics: Personalization of Cancer Medicine

Key Points

- Both Germline and Somatic Genetic and Epigenetic Information will Impact Cancer Risk Stratification, Screening, Early Detection, Diagnosis, Prevention, and Treatment
- Genetic/Epigenetic Biomarkers as New Tests that Improve Efficacy, Safety, and Cost-Effectiveness of Cancer Care