Intro to Cancer Genomics

John Welch, MD/PhD
Nixon Signs $1.6 Billion Cancer Bill, Names Man to Head Fight

WASHINGTON (UPI) -- President Nixon today signed into law a $1.6 billion program to find a cure for cancer. The act was "a milestone in the long and difficult effort to find the cause and cure of cancer." This law is...
What is cancer? – re Google images
What is cancer?

Survival: Colon Cancer

<table>
<thead>
<tr>
<th>Estimated New Cases*</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>238,590</td>
<td>28%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>118,080</td>
<td>14%</td>
</tr>
<tr>
<td>Colorectum</td>
<td>73,680</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>54,610</td>
<td>6%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>45,060</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,430</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>37,600</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>29,620</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>27,880</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,740</td>
<td>3%</td>
</tr>
<tr>
<td>All Sites</td>
<td>854,790</td>
<td>100%</td>
</tr>
<tr>
<td>Breast</td>
<td>232,340</td>
<td>29%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>110,110</td>
<td>14%</td>
</tr>
<tr>
<td>Colorectum</td>
<td>69,140</td>
<td>9%</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>49,560</td>
<td>6%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>45,310</td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>32,140</td>
<td>4%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>31,630</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>24,720</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,480</td>
<td>3%</td>
</tr>
<tr>
<td>Ovary</td>
<td>22,240</td>
<td>3%</td>
</tr>
<tr>
<td>All sites</td>
<td>805,500</td>
<td>100%</td>
</tr>
</tbody>
</table>

What is cancer?

Too many dividing cells
Too big
Too much nucleus
Too much disorder
Too little respect for boundaries

Image Fred Hutchinson Cancer Research Center
Fhcrc.org
What causes cancer?

Not eating enough organic vegetables?
Not exercising enough?
Getting old?
Dysorganized methylation?
Dysorganized gene expression?
Altered microRNAs?
DNA mutation?

Cancer Incidence by Age 2004-2008

SEER data.
What causes cancer?
Loss of tumor suppressors, Gain of oncogenes
How do you get mutations?

Examples of Dominantly Inherited Cancer Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Associated Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial retinoblastoma</td>
<td>RB1</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>TP53 (p53 protein)</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
<td>MLH1, MSH2, MSH6 PMS1, PMS2</td>
</tr>
<tr>
<td>Wilms’ tumor</td>
<td>WT1</td>
</tr>
<tr>
<td>Breast and ovarian cancer</td>
<td>BRCA1, BRCA2</td>
</tr>
<tr>
<td>von Hippel-Lindau</td>
<td>VHL</td>
</tr>
<tr>
<td>Cowden</td>
<td>PTEN</td>
</tr>
</tbody>
</table>

Only 5-10% of cancers are associated with hereditary disorders
Acquired mutations

Example: Translocation of *Bcr-Abl* Genes

Fusion protein with tyrosine kinase activity
How do you know it is an acquired mutation?

• Different from reference?
  – Works well for karyotypic changes

• ~1 million SNPs between individuals
  – Compare tumor vs germline
  – Blood or skin

• Expression and epigenetic changes
  – What to use as comparator?
Clonality imputed from Variant Allele Frequency (VAF)

Normal cells

Tumor cells

Clonality = 80% cells with a U2AF1 mutation

Next-Gen Sequencing (Genome, Exome, RNA)

40% VAF

Copy Number adjust X2

Matt Walter
Subclonal architecture
Evolution of Karyotypes in Acute Nonlymphocytic Leukemia\textsuperscript{1}

Joseph R. Testa,\textsuperscript{2} Uri Mintz, Janet D. Rowley, James W. Vardiman, and Harvey M. Golomb

[\textit{CANCER RESEARCH} 39, 3619–3627, September 1979]
Where are cancer mutations in the genome?

% of the Human Genome in Each Tier

- Tier 1: Exons: 48.7%
- Tier 2: Conserved: 1.3%
- Tier 3: Non-repetitive: 41.4%
- Tier 4: Repetitive: 8.6%
How do you identify oncogenic mutations?
How do you identify oncogenic mutations?

• Somatic vs inherited
  – How do you know it is somatic?
• Observed in many patients
  – Hot spots
• Associated with a specific form of cancer
  – Chronic myeloid leukemia only
• Present at relapse
• Makes biological sense
• Recapitulates disease in mice
Unsupervised clustering based on mutation status of SMGs.

Mutational organization

Themes in cancer

• Cancer is too much growth, not enough differentiation, and no respect for boundaries.

• Cancer is heterogeneous
  – Diverse types of cancer (cell of origin, clinical presentation)

• Cancer is associated with mutations
  – Again, lots of inter-patient heterogeneity
  – Does this account for clinical heterogeneity?
  – Clonal evolution ... a likely source of relapse disease.
Challenges in Cancer Genomics

• Identify mutations that are pathogenic
  • Move beyond tumor suppressors vs oncogenes
• Understand how mutations arise and organize
• Understand which mutations lead to poor outcomes, and which are sensitive to what drugs
• Integrate this understanding into clinical trials.